PUB-NO: US005516894A
DOCUMENT-IDENTIFIER: US 5516894 A
TITLE: A2b-adenosine receptors

PUBN-DATE: May 14, 1996

INVENTOR-INFORMATION:

NAME	COUNTRY
REPPERT, STEVEN M	US

INT-CL (IPC): C07K 14/705; F12N 15/12
EUR-CL (EPC): C07K014/705

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

10. Document ID: AU 200080348 A, WO 200116134 A1

L1: Entry 10 of 18 File: DWPI Mar 26, 2001

DERWENT-ACC-NO: 2001-257695
DERWENT-WEEK: 200137
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TITLE: New xanthine derivatives are selective A2B adenosine receptor antagonists, useful for treating e.g. diarrhea, asthma, Alzheimer's disease, Parkinson's disease, shock, depression and AIDS

INVENTOR: BIAGGIONI, I O; FEOKTISTOV, I A ; WELLS, J N

PRIORITY-DATA: 1999US-0151649 (August 31, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200080348 A	March 26, 2001	N/A	000	C07D473/06
WO 200116134 A1	March 8, 2001	E	024	C07D473/06

INT-CL (IPC): A61K 31/522; A61P 1/12; A61P 11/06; C07D 473/06

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Clip Img | Image

Generate Collection

Term	Documents
A2B.DWPI,EPAB,JPAB,USPT,PGPB.	537
A2BS.DWPI,EPAB,JPAB,USPT,PGPB.	4
ANTAGONIST.DWPI,EPAB,JPAB,USPT,PGPB.	32672
ANTAGONISTS.DWPI,EPAB,JPAB,USPT,PGPB.	36383
ADENOSINE.DWPI,EPAB,JPAB,USPT,PGPB.	16034
ADENOSINES.DWPI,EPAB,JPAB,USPT,PGPB.	323
((A2B SAME ANTAGONIST) AND (ADENOSINE SAME ANTAGONIST)).USPT,PGPB,JPAB,EPAB,DWPI.	18

Display 10 Documents, starting with Document: 11

Display Format: CIT Change Format

WEST

Generate Collection

L1: Entry 17 of 18 File: DWPI May 14, 1996

DERWENT-ACC-NO: 1996-251087
DERWENT-WEEK: 199625
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TITLE: Recombinant polypeptide(s) encoding new A2b adenosine receptors - used to screen candidate compounds for antagonist activity for use in treatment of inflammatory gastrointestinal tract diseases and asthma

ABTX:
USE - The polypeptide is an A2b-adenosine receptor. The receptor, fragments and analogues can be used in screens of candidate compounds for their ability to antagonise the interaction between adenosine and the A2b-receptor. Antibodies specific for the receptor can also be prepared and used in therapy and in diagnosis. The antagonists and antibodies can be used in pharmaceuticals for the reductions of inflammatory gastrointestinal tract diseases, or in the treatment of asthma.

TTX:
RECOMBINATION POLYPEPTIDE ENCODE NEW ADENOSINE RECEPTOR SCREEN CANDIDATE COMPOUND ANTAGONIST ACTIVE TREAT INFLAMMATION GASTRO TRACT DISEASE ASTHMA

WEST

Generate Collection

Search Results - Record(s) 11 through 18 of 18 returned.

11. Document ID: AU 200053160 A, WO 200073307 A2

L1: Entry 11 of 18 File: DWPI Dec 18, 2000

DERWENT-ACC-NO: 2001-070956
DERWENT-WEEK: 200118
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TITLE: New 8-phenylxanthine derivatives are adenosine-2B antagonists useful for treating e.g. asthma, diarrheal diseases, insulin resistance, diabetes, cancer, ischemia and reperfusion injuries and diabetic retinopathy

INVENTOR: JACOBSON, K A; KIM, Y ; LINDEN, J M

PRIORITY-DATA: 1999US-0151875 (August 31, 1999), 1999US-0136898 (June 1, 1999), 1999US-0136900 (June 1, 1999), 1999US-0505504 (June 1, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200053160 A	December 18, 2000	N/A	000	C07D473/00
WO 200073307 A2	December 7, 2000	E	107	C07D473/00

INT-CL (IPC): C07D 473/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Clip Img | Image

12. Document ID: US 6060481 A

L1: Entry 12 of 18 File: DWPI May 9, 2000

DERWENT-ACC-NO: 2000-349698
DERWENT-WEEK: 200030
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TITLE: Method for improving insulin sensitivity comprises administration of an adenosine-2B antagonist which is preferably xanthine derivative

INVENTOR: CRIST, G H; LANOUE, K F ; LINDEN, J M

PRIORITY-DATA: 1999US-0259201 (March 1, 1999), 1998US-0086101 (May 28, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6060481 A	May 9, 2000	N/A	022	A61K031/52

INT-CL (IPC): A61K 31/52

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

13. Document ID: EP 1011608 A2, WO 9963938 A2, AU 9946756 A

L1: Entry 13 of 18 File: DWPI Jun 28, 2000

DERWENT-ACC-NO: 2000-116433
DERWENT-WEEK: 200035
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TITLE: Novel composition for treating or preventing e.g. cardiopulmonary and renal injury

INVENTOR: HILL, J L; NYCE, J W

PRIORITY-DATA: 1998US-0093972 (June 9, 1998), 1998US-0088501 (June 8, 1998), 1998US-0089657 (June 9, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1011608 A2	June 28, 2000	E	000	A61K006/00
WO 9963938 A2	December 16, 1999	E	251	A61K000/00
AU 9946756 A	December 30, 1999	N/A	000	A61K000/00

INT-CL (IPC): A61K 0/00; A61K 6/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

14. Document ID: EP 1082120 A1, WO 9962518 A1, AU 9942265 A, BR 9911612 A, NO 200006090 A

L1: Entry 14 of 18 File: DWPI Mar 14, 2001

DERWENT-ACC-NO: 2000-147035
DERWENT-WEEK: 200116
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TITLE: New N-6 substituted 7-deazapurine for treating gastrointestinal and respiratory disorders

INVENTOR: CASTELHANO, A L; MCKIBBEN, B ; WITTER, D J

PRIORITY-DATA: 1999US-0126527 (March 26, 1999), 1998US-0087702 (June 2, 1998), 1999US-0123216 (March 8, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1082120 A1	March 14, 2001	E	000	A61K031/505
WO 9962518 A1	December 9, 1999	E	169	A61K031/505
AU 9942265 A	December 20, 1999	N/A	000	A61K031/505
BR 9911612 A	February 6, 2001	N/A	000	A61K031/505
NO 200006090 A	January 31, 2001	N/A	000	A61K000/00

INT-CL (IPC): A61K 0/00; A61K 31/505; C07D 487/04

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Clip Img | Image

☐ 15. Document ID: US 6117878 A, WO 9942093 A2, AU 9928759 A

L1: Entry 15 of 18 File: DWPI Sep 12, 2000

DERWENT-ACC-NO: 1999-518502
DERWENT-WEEK: 200046
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TITLE: Use of adenosine A2B receptor subtype specific inhibitor for treating e.g. inflammation, allergies, ashthma etc.

INVENTOR: LINDEN, J M

PRIORITY-DATA: 1998US-0027649 (February 24, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6117878 A	September 12, 2000	N/A	000	A61K031/52
WO 9942093 A2	August 26, 1999	E	026	A61K031/00
AU 9928759 A	September 6, 1999	N/A	000	A61K031/00

INT-CL (IPC): A61K 31/00; A61K 31/52

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Clip Img | Image

☐ 16. Document ID: US 5854081 A

L1: Entry 16 of 18 File: DWPI Dec 29, 1998

DERWENT-ACC-NO: 1999-094922
DERWENT-WEEK: 199908
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TITLE: Detecting binding of tritiated 1,3-di:ethyl-8-phenyl-xanthine - to human A2B adenosine receptors

INVENTOR: JIN, X; LINDEN, J ; ROBEVA, A ; TAYLOR, H ; WOODARD, R

PRIORITY-DATA: 1996US-0670175 (June 20, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5854081 A	December 29, 1998	N/A	024	G01N033/566

INT-CL (IPC): G01N 33/566

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

☑ 17. Document ID: US 5516894 A

L1: Entry 17 of 18 File: DWPI May 14, 1996

DERWENT-ACC-NO: 1996-251087
DERWENT-WEEK: 199625
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Recombinant polypeptide(s) encoding new A2b adenosine receptors - used to screen candidate compounds for antagonist activity for use in treatment of inflammatory gastrointestinal tract diseases and asthma

INVENTOR: REPPERT, S M

PRIORITY-DATA: 1992US-0850188 (March 11, 1992), 1994US-0293563 (August 22, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5516894 A	May 14, 1996	E	031	C07K014/705

INT-CL (IPC): C07K 14/705; C12N 15/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

☑ 18. Document ID: JP 08500967 W, WO 9325677 A1, AU 9342966 A, EP 644935 A1

L1: Entry 18 of 18 File: DWPI Feb 6, 1996

DERWENT-ACC-NO: 1994-007535
DERWENT-WEEK: 199643
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: DNA sequences encoding the human A1, A2a and A2b adenosine receptors - for screening for anti-hypertensives, hypnotics, anti-psychotics, bronchodilators and for recombinant receptor prodn.

INVENTOR: FURLONG, T; PIERCE, K D ; SEIBIE, L ; SHINE, J ; TOWNSEND-NICHOLSON, C A ; SELBIE, L

PRIORITY-DATA: 1992AU-0002936 (June 12, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 08500967 W	February 6, 1996	N/A	028	C12N015/09
WO 9325677 A1	December 23, 1993	E	026	C12N015/12
AU 9342966 A	January 4, 1994	N/A	000	C12N015/12
EP 644935 A1	March 29, 1995	E	000	C12N015/12

INT-CL (IPC): C12N 15/09; C12N 15/12; C12P 21/02; C12P 21/02; C12R 1/91

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

Generate Collection

Term	Documents
A2B.DWPI,EPAB,JPAB,USPT,PGPB.	537
A2BS.DWPI,EPAB,JPAB,USPT,PGPB.	4
ANTAGONIST.DWPI,EPAB,JPAB,USPT,PGPB.	32672
ANTAGONISTS.DWPI,EPAB,JPAB,USPT,PGPB.	36383
ADENOSINE.DWPI,EPAB,JPAB,USPT,PGPB.	16034
ADENOSINES.DWPI,EPAB,JPAB,USPT,PGPB.	323
((A2B SAME ANTAGONIST) AND (ADENOSINE SAME ANTAGONIST)).USPT,PGPB,JPAB,EPAB,DWPI.	18

Display 10 Documents, starting with Document: 18

Display Format: CIT Change Format

2/3,AB/9 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12203209 BIOSIS NO.: 199900498058
Adenosine **receptor** activation induces vascular endothelial growth factor in human retinal endothelial cells.
AUTHOR: Grant Maria B(a); Tarnuzzer Roy W; Caballero Sergio; Ozeck Mark J; Davis Margaret I; Spoerri Polyxenie E; Feoktistov Igor; Biaggioni Italo; Shryock John C; Belardinelli Luiz
AUTHOR ADDRESS: (a)Department of Medicine, Division of Endocrinology and Metabolism, University of Florida, Gainesville, FL, 32610-0226**USA
JOURNAL: Circulation Research 85 (8):p699-706 Oct. 15, 1999
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine, released in increased amounts by hypoxic tissues, is thought to be an angiogenic factor that links altered cellular metabolism caused by oxygen deprivation to compensatory angiogenesis. Adenosine interacts with 4 subtypes of G protein-coupled **receptors**, termed A1, A2A, **A2B**, and A3. We investigated whether adenosine causes proliferation of human retinal endothelial cells (HRECs) and synthesis of vascular endothelial growth factor (VEGF) and, if so, which adenosine **receptor** subtype mediates these effects. The nonselective adenosine **receptor** agonist 5'-N-ethylcarboxamidoadenosine (NECA), in a concentration-dependent manner, increased both VEGF mRNA and protein expression by HRECs, as well as proliferation. This proliferative effect of NECA was inhibited by the addition of anti-human VEGF antibody. NECA also increased insulin-like growth factor-I and basic fibroblast growth factor mRNA expression in a time-dependent manner and cAMP accumulation in these cells. In contrast, neither the A1 agonist N6-cyclopentyladenosine nor the A2A agonist 2-p-(2-carboxyethyl) phenethylamino-NECA caused any of the above effects of NECA. The effects of NECA were not significantly attenuated by either the A2A antagonist SCH58261 or the A1 antagonist 8-cyclopenthyl-1,3-dipropylxanthine. However, the nonselective adenosine **receptor** antagonist xanthine amine congener completely inhibited the effects of NECA. Addition of **antisense** oligonucleotide complementary to **A2B** adenosine **receptor** mRNA inhibited VEGF protein production by HRECs after NECA stimulation. Thus, the **A2B** adenosine **receptor** subtype appears to mediate the actions of adenosine to increase growth factor production, cAMP content, and cell proliferation of HRECs. Adenosine activates the **A2B** adenosine **receptor** in HRECs, which may lead to neovascularization by a mechanism involving increased angiogenic growth factor expression.

antisense strategy to target the nonvisual arrestins, arrestin-2 and arrestin-3, and determined the associated effects on the regulation of G protein-coupled **receptor** (GPCR) signaling. HEK293 cells stably expressing **antisense** constructs targeting arrestin-2 exhibited a selective reduction (approximately 50%) in arrestin-2 levels, while arrestin-3 **antisense** constructs resulted in reductions (>/=50%) in both arrestin-2 and arrestin-3 levels. Initial analysis of these cells demonstrated that a reduced level of arrestin expression resulted in a significant decrease in the extent of agonist-induced internalization of exogenously expressed beta2ARs, but had no effect on internalization of either m2 or m3 muscarinic acetylcholine **receptors** . Additional characterization involved assessing the role of arrestins in the regulation of endogenous GPCRs in these cells. Reduced arrestin levels significantly decreased the rate of endogenous beta2AR internalization, desensitization, and resensitization. Further analysis demonstrated that the desensitization of endogenous **A2b** adenosine and prostaglandin E2-stimulated **receptors** was also attenuated in cells with reduced arrestin levels. The effects on the beta2-adrenergic, **A2b** adenosine, and PGE2-stimulated **receptors** were similar among cell lines that exhibited either a selective reduction in arrestin-2 levels or a reduction in both arrestin-2 and -3 levels. These findings establish the utility of **antisense** approaches in the examination of arrestin-mediated GPCR regulation.

2/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09740482 98035703 PMID: 9367639
Localization of adenosine **receptor** messenger RNAs in the rat eye.
Kvanta A; Seregard S; Sejersen S; Kull B; Fredholm BB
Department of Ophthalmology, St Erik's Eye Hospital, Stockholm, Sweden.
Experimental eye research (ENGLAND) Nov 1997, 65 (5) p595-602,
ISSN 0014-4835 Journal Code: EPL
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine is present in all cells and body fluids and has been suggested to play several roles in the physiology of ocular tissues. The present study was undertaken to determine which types of adenosine **receptor** mRNAs are present in the rat eye, and where they are expressed. RNA or deoxyoligodeoxynucleotides complementary to rat adenosine **receptor** subtypes A1, A2A, **A2B** and A3 were used to generate 35S labeled **antisense** and sense probes. The probes were then used for in situ hybridization on 10 microm cryosections of the rat eye including the cornea, iris, ciliary body, lens, retina, choroid and sclera. A1, A2A and **A2B** **receptor** mRNAs were demonstrated in the ciliary processes. A1 **receptor** mRNA was also expressed in the ganglion cell layer of the retina. The retina also showed A2A **receptor** mRNA expression, which was most prominent in the inner nuclear layer and less prominent in the ganglion cell layer and outer nuclear layer. Weak A2A expression was found in the retinal pigment epithelium and choriocapillaris. No significant expression of A3 **receptor** mRNA was found in the rat eye. In conclusion, using in situ hybridization, we have demonstrated expression of mRNA for A1, A2A and **A2B** adenosine **receptors** in the rat eye. The expression patterns support specific roles for adenosine in the ciliary process and retina. Copyright 1997 Academic Press Limited.

2/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09201429 97070852 PMID: 8913778
Cyclooxygenase-2 expression in rat microglia is induced by adenosine A2a-**receptors**.

Fiebich BL; Biber K; Lieb K; van Calker D; Berger M; Bauer J; Gebicke-Haerter PJ

Abt. Psychiatrie, Universitat Freiburg, Germany.

Glia (UNITED STATES) Oct 1996, 18 (2) p152-60, ISSN 0894-1491 Journal Code: GLI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We investigated the regulation of COX-2 expression and activity by adenosine **receptors** in rat microglial cells. The selective adenosine A2a-**receptor** agonist CGS21680 and the non-selective adenosine A1- and A2-**receptor** agonist 5'-N-ethylcarboxiamidoadenosine (NECA) induced an increase in COX-2 mRNA levels and the synthesis of prostaglandin E2 (PGE2). The adenosine A1-**receptor** agonist cyclopentyladenosine (CPA) was less potent, and the adenosine A1-**receptor** -specific agonist N6-2-(-aminophenylo)ethyladenosine (APNEA) showed only marginal effects. Microglia expressed adenosine A1-, A2a-, and A3-, but not **A2b-receptor** mRNAs, whereas astroglial cells expressed adenosine **A2b-** but not A2a-**receptor** mRNA. The adenosine A2a-**receptor** selective antagonist (E)-8-(3,4-dimethoxystyryl)-1,3-dipropy l-7-methylxanthine (KF17837) inhibited both CGS21680-induced COX-2 expression and PGE2 release. CGS21680-increased PGE2 levels were inhibited by dexamethasone, by the nonsteroidal antiinflammatory drug meloxicam, and by the adenylyl cyclase inhibitor 9-(tetrahydro-2-furanyl)-9H-purine-6-amin e (SQ22536). CGS21680 and NECA both increased intracellular cAMP levels in microglial cells. Dibutyryl cAMP as well as forskolin induced the release of PGE2. The results strongly suggest that adenosine A2a-**receptor** -induced intracellular signaling events cause an up-regulation of the COX-2 gene and the release of PGE2. Apparently, the cAMP second messenger system plays a crucial role in COX-2 gene regulation in rat microglial cells. The results are discussed with respect to neurodegenerative disorders of the CNS such as Alzheimer's disease, in which activated microglia are critically involved and COX inhibitors may be of therapeutic benefit.

2/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09108828 96428971 PMID: 8832073

Tissue distribution of adenosine **receptor** mRNAs in the rat.

Dixon AK; Gubitz AK; Sirinathsinghji DJ; Richardson PJ; Freeman TC

Department of Pharmacology, University of Cambridge.

British journal of pharmacology (ENGLAND) Jul 1996, 118 (6) p1461-8, ISSN 0007-1188 Journal Code: B00

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

1. A degree of ambiguity and uncertainty exists concerning the distribution of mRNAs encoding the four cloned adenosine **receptors**. In order to consolidate and extent current understanding in this area, the expression of the adenosine **receptors** has been examined in the rat by use of in situ hybridisation and the reverse transcription-polymerase chain reaction (RT-PCR). 2. In accordance with earlier studies, in situ hybridisation revealed that the adenosine A1 **receptor** was widely expressed in the brain, whereas A2A **receptor** mRNA was restricted to the striatum, nucleus accumbens and olfactory tubercle. In addition, A1 **receptor** mRNA was detected in large striatal cholinergic interneurones, 26% of these neurones were also found to express the A2A **receptor** gene. Central levels of mRNAs encoding adenosine **A2B** and A3 **receptors** were, however, below the detection limits of in situ hybridisation. 3. The more sensitive technique of RT-PCR was then employed to investigate the distribution of adenosine **receptor** mRNAs in the central nervous system (CNS) and a wide range of peripheral tissues. As a result, many novel sites of adenosine **receptor** gene expression were identified. A1 **receptor** expression has now been found in the

s a2b and receptor? and (antisense? or ribozym?)

	742	A2B
	1128286	RECEPTOR?
	20243	ANTISENSE?
	5255	RIBOZYM?
S1	13	A2B AND RECEPTOR? AND (ANTISENSE? OR RIBOZYM?)

? rd

...completed examining records

S2	9	RD (unique items)

? t s2/3,ab/all

2/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11281051 21155461 PMID: 11230251
A(2B) **receptors** mediate the antimitogenic effects of adenosine in cardiac fibroblasts.
Dubey RK; Gillespie DG; Zacharia LC; Mi Z; Jackson EK
Center for Clinical Pharmacology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. raghvendra.dubey@fhk.usz.ch
Hypertension (United States) Feb 2001, 37 (2) p716-21, ISSN 1524-4563 Journal Code: DCZ
Contract/Grant No.: HL-35909, HL, NHLBI; HL-55314, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine inhibits growth of cardiac fibroblasts; however, the adenosine **receptor** subtype that mediates this antimitogenic effect remains undefined. Therefore, the goals of this study were to determine which adenosine **receptor** subtype mediates the antimitogenic effects of adenosine and to investigate the signal transduction mechanisms involved. In rat left ventricular cardiac fibroblasts, PDGF-BB (25 ng/mL) stimulated DNA synthesis ((3)H-thymidine incorporation), cellular proliferation (cell number), collagen synthesis ((3)H-proline incorporation), and MAP kinase activity. The adenosine **receptor** agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N(6)-cyclopentyladenosine, 4-aminobenzyl-5'-N-methylcarboxamidoadenosine, or CGS21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an A(2B) **receptor**-mediated effect. The adenosine **receptor** antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an antagonist profile consistent with an A(2) **receptor**-mediated effect. **Antisense**, but not sense or scrambled, oligonucleotides to the A(2B) **receptor** stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and collagen synthesis. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of adenosine deaminase and adenosine kinase, respectively) were abolished by **antisense**, but not scrambled or sense, oligonucleotides to the A(2B) **receptor**. Our findings strongly support the hypothesis that adenosine causes inhibition of CF growth by activating A(2B) **receptors** coupled to inhibition of MAP kinase activity. Thus, A(2B) **receptors** may play a critical role in regulating cardiac remodeling associated with CF proliferation. Pharmacologic or molecular biological activation of A(2B)

receptors may p[redacted]ent cardiac remodeling a[redacted]ciated with hypertension, myoca[redacted]al infarction, and myocardi[redacted] reperfusion injury after ischemia.

2/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10843595 20496761 PMID: 11041847
Arrestin isoforms dictate differential kinetics of **A2B** adenosine **receptor** trafficking.
Mundell SJ; Matharu AL; Kelly E; Benovic JL
Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.
Biochemistry (UNITED STATES) Oct 24 2000, 39 (42) p12828-36, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: GM47417, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine mediates the activation of adenylyl cyclase via its interaction with specific A(2A) and A(2B) adenosine **receptors**. Previously, we demonstrated that arrestins are involved in rapid agonist-promoted desensitization of the A(2B) adenosine **receptor** (A(2B)AR) in HEK293 cells. In the present study, we investigate the role of arrestins in A(2B)AR trafficking. Initial studies demonstrated that HEK293 cells stably expressing arrestin **antisense** constructs, which reduce endogenous arrestin levels, effectively reduced A(2B)AR internalization. A(2B)AR recycling after agonist-induced endocytosis was also significantly impaired in cells with reduced arrestin levels. Interestingly, while overexpression of arrestin-2 or arrestin-3 rescued A(2B)AR internalization and recycling, arrestin-3 promoted a significantly faster rate of recycling as compared to arrestin-2. The specificity of arrestin interaction with A(2B)ARs was further investigated using arrestins fused to the green fluorescent protein (arr-2-GFP and arr-3-GFP). Both arrestins underwent rapid translocation (<1 min) from the cytosol to the plasma membrane following A(2B)AR activation. However, longer incubations with agonist (>10 min) revealed that arr-2-GFP but not arr-3-GFP colocalized with the A(2B)AR in rab-5 and transferrin **receptor** containing early endosomes. At later times, the A(2B)AR but not arr-2-GFP was observed in an apparent endocytic recycling compartment. Thus, while arrestin-2 and arrestin-3 mediate agonist-induced A(2B)AR internalization with relative equal potency, arrestin isoform binding dictates the differential kinetics of A(2B)AR recycling and resensitization.

2/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10338776 99321508 PMID: 10393547
Characterization of G protein-coupled **receptor** regulation in **antisense** mRNA-expressing cells with reduced arrestin levels.
Mundell SJ; Loudon RP; Benovic JL
Department of Microbiology and Immunology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.
Biochemistry (UNITED STATES) Jul 6 1999, 38 (27) p8723-32, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: GM47417, GM, NIGMS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Previous studies with overexpressing wild-type or dominant negative nonvisual arrestins have established a role for these proteins in beta2-adrenergic **receptor** (beta2AR) internalization, desensitization, and resensitization. To validate and extend such findings, we employed an

heart, aorta, liver, kidney, eye and bladder. These observations are largely consistent with previous functional data. A2A **receptor** mRNA was detected in all brain regions tested, demonstrating that expression of this **receptor** is not restricted to the basal ganglia. In the periphery A2A **receptor** mRNA was also found to be more widely distributed than generally recognised. The ubiquitous distribution of the **A2B receptor** is shown for the first time, **A2B** mRNA was detected at various levels in all rat tissues studied. Expression of the gene encoding the adenosine A3 **receptor** was also found to be widespread in the rat, message detected throughout the CNS and in many peripheral tissues. This pattern of expression is similar to that observed in man and sheep, which had previously been perceived to possess distinct patterns of A3 **receptor** gene expression in comparison to the rat. 4. In summary, this work has comprehensively studied the expression of all the cloned adenosine **receptors** in the rat, and in so doing, resolves some of the uncertainty over where these **receptors** might act to control physiological processes mediated by adenosine.

2/3,AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13000014 BIOSIS NO.: 200100207163
A2B receptors mediate the antimitogenic effects of adenosine in cardiac fibroblasts.
AUTHOR: Dubey Raghvendra K(a); Gillespie Delbert G; Zacharia Lefteris C; Mi Zaichuan; Jackson Edwin K
AUTHOR ADDRESS: (a)Department of Obstetrics and Gynecology, Clinic for Endocrinology, Frauenklinik, University Hospital Zurich, D215, NORD-1, 8091, Zurich: raghvendra.dubey@fhk.usz.ch**Switzerland
JOURNAL: Hypertension (Baltimore) 37 (2 Part 2):p716-721 February, 2001
MEDIUM: print
ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine inhibits growth of cardiac fibroblasts; however, the adenosine **receptor** subtype that mediates this antimitogenic effect remains undefined. Therefore, the goals of this study were to determine which adenosine **receptor** subtype mediates the antimitogenic effects of adenosine and to investigate the signal transduction mechanisms involved. In rat left ventricular cardiac fibroblasts, PDGF-BB (25 ng/mL) stimulated DNA synthesis (3H-thymidine incorporation), cellular proliferation (cell number), collagen synthesis (3H-proline incorporation), and MAP kinase activity. The adenosine **receptor** agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N6-cyclopentyladenosine, 4-aminobenzyl-5'-N-methylcarboxamidoadenosine, or CGS21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an **A2B receptor**-mediated effect. The adenosine **receptor** antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an antagonist profile consistent with an A2 **receptor**-mediated effect. **Antisense**, but not sense or scrambled, oligonucleotides to the **A2B receptor** stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and collagen synthesis. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of adenosine deaminase and adenosine kinase, respectively) were abolished by **antisense**, but not scrambled or sense, oligonucleotides to the **A2B receptor**.

Our findings strongly support the hypothesis that adenosine causes inhibition of CF growth by activating **A2B receptors** coupled to inhibition of MAP kinase activity. Thus, **A2B receptors** may play a critical role in regulating cardiac remodeling associated with CF proliferation. Pharmacologic or molecular biological activation of **A2B receptors** may prevent cardiac remodeling associated with hypertension, myocardial infarction, and myocardial reperfusion injury after ischemia.

2001

2/3,AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

12368160 BIOSIS NO.: 200000121662
A2B receptors mediate antimitogenesis in vascular smooth muscle cells.
AUTHOR: Dubey Raghvendra K(a); Gillespie Delbert G; Shue Holly; Jackson Edwin K
AUTHOR ADDRESS: (a)Center for Clinical Pharmacology, University of Pittsburgh Medical Center, 200 Lothrop St, 623 Scaife Hall, Pittsburgh, PA, 15213-2582**USA
JOURNAL: Hypertension (Baltimore) 35 (1 Part 2):p267-272 Jan., 2000
ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine inhibits growth of vascular smooth muscle cells. The goals of this study were to determine which adenosine **receptor** subtype mediates the antimitogenic effects of adenosine and to investigate the signal transduction mechanisms involved. In rat aortic vascular smooth muscle cells, platelet-derived growth factor-BB (PDGF-BB) (25 ng/mL) stimulated DNA synthesis ((3H)thymidine incorporation), cellular proliferation (cell number), collagen synthesis ((3H)proline incorporation), total protein synthesis ((3H)leucine incorporation), and mitogen-activated protein (MAP) kinase activity. The adenosine **receptor** agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N6-cyclopentyladenosine or CGS21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an **A2B receptor**-mediated effect. The adenosine **receptor** antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an antagonist profile consistent with an A2 **receptor**-mediated effect. **Antisense**, but not sense or scrambled, oligonucleotides to the **A2B receptor** stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and MAP kinase activity. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of adenosine deaminase and adenosine kinase, respectively) were abolished by **antisense**, but not scrambled or sense, oligonucleotides to the **A2B receptor**. Our findings strongly support the hypothesis that adenosine causes inhibition of vascular smooth muscle cell growth by activating **A2B receptors** coupled to inhibition of MAP kinase activity. Pharmacological or molecular biological activation of **A2B receptors** may prevent vascular remodeling associated with hypertension, atherosclerosis, and restenosis following balloon angioplasty.

WEST

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Search Results - Record(s) 1 through 10 of 18 returned.

1. Document ID: US 6270766 B1

L1: Entry 1 of 18 File: USPT Aug 7, 2001

US-PAT-NO: 6270766
DOCUMENT-IDENTIFIER: US 6270766 B1

TITLE: Anti-TNF antibodies and methotrexate in the treatment of arthritis and crohn's disease

DATE-ISSUED: August 7, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Feldman; Marc	Highgate	N/A	N/A	GBX
Maini; Ravinder N.	London	N/A	N/A	GBX

US-CL-CURRENT: 424/145.1; 424/130.1, 424/133.1, 424/152.1, 424/158.1, 424/172.1, 424/184.1, 424/192.1, 514/2, 514/8, 514/885

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

2. Document ID: US 6207876 B1

L1: Entry 2 of 18 File: USPT Mar 27, 2001

US-PAT-NO: 6207876
DOCUMENT-IDENTIFIER: US 6207876 B1

TITLE: Adenosine deaminase deficient transgenic mice and methods for the use thereof

DATE-ISSUED: March 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kellems; Rodney E.	Houston	TX	N/A	N/A
Datta; Surjit K.	Houston	TX	N/A	N/A
Blackburn; Michael R.	Pearland	TX	N/A	N/A

US-CL-CURRENT: 800/18; 435/320.1, 435/325, 435/455, 800/22, 800/9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

3. Document ID: US 6166181 A

L1: Entry 3 of 18 File: USPT Dec 26, 2000

US-PAT-NO: 6166181
DOCUMENT-IDENTIFIER: US 6166181 A

TITLE: Human adenosine receptors

DATE-ISSUED: December 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobson; Marlene A.	Elkins Park	PA	N/A	N/A
Luneau; Christopher J.	Lansdale	PA	N/A	N/A
Johnson; Robert G.	Rosemont	PA	N/A	N/A
Salvatore; Christopher A.	North Wales	PA	N/A	N/A

US-CL-CURRENT: 530/350; 435/252.3, 435/320.1, 435/69.1, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

4. Document ID: US 6117878 A

L1: Entry 4 of 18 File: USPT Sep 12, 2000

US-PAT-NO: 6117878
DOCUMENT-IDENTIFIER: US 6117878 A

TITLE: 8-phenyl- or 8-cycloalkyl xanthine antagonists of A2B human adenosine receptors

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Linden; Joel M.	Charlottesville	VA	N/A	N/A

US-CL-CURRENT: 514/263

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

5. Document ID: US 5817760 A

L1: Entry 5 of 18 File: USPT Oct 6, 1998

US-PAT-NO: 5817760
DOCUMENT-IDENTIFIER: US 5817760 A

TITLE: Human A3 adenosine receptors

DATE-ISSUED: October 6, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobson; Marlene A.	Elkins Park	PA	N/A	N/A
Luneau; Christopher J.	Lansdale	PA	N/A	N/A
Johnson; Robert G.	Rosemont	PA	N/A	N/A
Salvatore; Christopher A.	North Wales	PA	N/A	N/A

US-CL-CURRENT: 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

6. Document ID: US 5780481 A

L1: Entry 6 of 18 File: USPT Jul 14, 1998

US-PAT-NO: 5780481
DOCUMENT-IDENTIFIER: US 5780481 A

TITLE: Method for inhibiting activation of the human A3 adenosine receptor to treat asthma

DATE-ISSUED: July 14, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobson; Marlene A.	Elkins Park	PA	N/A	N/A
Norton; Richard	Somerset	NJ	N/A	N/A
Chakravarty; Prasun K.	Edison	NJ	N/A	N/A

US-CL-CURRENT: 514/293; 514/294, 514/359, 514/461

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

7. Document ID: US 5646156 A

L1: Entry 7 of 18 File: USPT Jul 8, 1997

US-PAT-NO: 5646156
DOCUMENT-IDENTIFIER: US 5646156 A

TITLE: Inhibition of eosinophil activation through A3 adenosine receptor antagonism

DATE-ISSUED: July 8, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobson; Marlene A.	Elkins Park	PA	N/A	N/A
Johnson; Robert G.	Rosemont	PA	N/A	N/A
Salvatore; Christopher A.	North Wales	PA	N/A	N/A

US-CL-CURRENT: 514/263; 514/826, 514/861, 514/863, 514/870, 514/886

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

☐ 8. Document ID: US 5599671 A

L1: Entry 5 of 18 File: USPT Feb 4, 1997

US-PAT-NO: 5599671
DOCUMENT-IDENTIFIER: US 5599671 A

TITLE: Human A2B adenosine receptor assay

DATE-ISSUED: February 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobson; Marlene A.	Elkins Park	PA	N/A	N/A
Luneau; Christopher J.	Lansdale	PA	N/A	N/A
Johnson; Robert G.	Rosemont	PA	N/A	N/A
Salvatore; Christopher A.	North Wales	PA	N/A	N/A

US-CL-CURRENT: 435/6; 435/252.3, 435/320.1, 435/69.1, 435/7.2, 435/7.21, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

☐ 9. Document ID: US 5516894 A

L1: Entry 9 of 18 File: EPAB May 14, 1996

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     S1        0  155, 5
? b 155, 5

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     $0.00  Estimated cost File410
     $0.05  TYMNET
     $0.05  Estimated cost this search
     $0.05  Estimated total session cost   0.341 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2001/Oct W2
  File   5:Biosis Previews(R)  1969-2001/Sep W2
         (c) 2001 BIOSIS

      Set  Items  Description
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? s a2b and adenosine and antagonist

            742  A2B
         179702  ADENOSINE
         212412  ANTAGONIST
      S1    177  A2B AND ADENOSINE AND ANTAGONIST
? rd

...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...completed examining records
      S2    139  RD (unique items)
? t s2/3,ab/all


 2/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11652680   99605634   PMID: 11542498
  Role of adenosine in asthma.
  Feoktistov I; Biaggioni I
  Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA.
  (UNITED STATES)  1996,  39  p333-6,  ISSN 0272-4391
  Contract/Grant No.: RR00095, RR, NCRR
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  Several lines of evidence support the hypothesis that adenosine
 contributes to asthma. Inhaled adenosine provokes
bronchoconstriction in asthmatics, but not in nonasthmatics. This process
appears to be mediated by mast cell activation, because it can be blocked
by antihistamines and inhibitors of mast cell activation. Inhaled
adenosine evokes release of mast cell mediators in bronchoalveolar
lavage fluid, including histamine, prostaglandin D2, and tryptase, a
specific mast cell marker. Also, adenosine potentiates the
immunological activation of mast cells in vitro, including rat peritoneal
mast cells, mouse bone marrow-derived mast cells, human lung mast cells,
and the human mast cell line HMC-1. The receptor subtype that mediates this
activation differs between mast cell type, but preliminary evidence
suggests that human lung mast cells express A2B receptors. An
argument against the contribution of adenosine in asthma has been the
```

"enprofylline paradox." This xanthine (3-(n-propylyl)xanthine) is as effective an antiasthmatic as theophylline (1,3-dimethylxanthine) but was initially thought not to be an **adenosine** receptor **antagonist**. More recent evidence has confirmed that enprofylline blocks **A2B** receptors with a Ki (7 microM) similar to that of theophylline (13 microM) and well within its therapeutic plasma levels (5-25 microM). This finding, we believe, resolves the enprofylline paradox and supports the hypothesis that **adenosine**, through **A2B** receptor activation, contributes to asthma. Preliminary evidence suggests that **A2B** receptors are indeed present in human lung mast cells. **A2B** receptors, therefore, may be a potential target for the development of antiasthmatic drugs.

2/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11637744 21413486 PMID: 11522605
Pharmacological characterization of **adenosine** receptors in PGT-beta mouse pineal gland tumour cells.
Suh BC; Kim TD; Lee JU; Seong JK; Kim KT
Department of Life Science, Division of Molecular and Life Science, Pohang University of Science and Technology, San 31, Hyoja-Dong, Pohang 790-784, Korea.
British journal of pharmacology (England) Sep 2001, 134 (1) p132-42, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
1. The **adenosine** receptor in mouse pinealocytes was identified and characterized using pharmacological and physiological approaches. 2. Expression of the two **adenosine** receptor subtypes **A2B** and A3 was detected in mouse pineal glands and PGT-beta cells by polymerase chain reaction and nucleotide sequencing. 3. **Adenosine** and 5'-N-ethylcarboxamidoadenosine (NECA) evoked cyclic AMP generation but the A2)-selective agonist 2-(4-(2-carboxyethyl)phenylethylamino)**adenosine** -5'-N-ethylcarboxamideadenosine (CGS 21680) and the A1-specific agonists R-N(6)-(2-phenylisopropyl)**adenosine** (R-PIA) and N(6)-cyclopentyladeno sine (CPA) had little effect on intracellular cyclic AMP levels. The **A2B** receptor selective antagonists alloxazine and enprofylline completely blocked NECA-mediated cyclic AMP accumulation. 4. Treatment of cells with the A3-selective agonist N(6)-(3-iodobenzyl)-5'-(N-methylcarbamo yl)**adenosine** (IB-MECA) inhibited the elevation of the cyclic AMP level induced by NECA or isoproterenol in a concentration-dependent manner with maximal inhibition of 40 - 50%. These responses were blocked by the specific A3 **adenosine** receptor **antagonist** MRS 1191. Pretreatment of the cells with pertussis toxin attenuated the IB-MECA-induced responses, suggesting that this effect occurred via the pertussis toxin-sensitive inhibitory G proteins. 5. IB-MECA also caused a concentration-dependent elevation in [Ca(2+)]i and IP3 content. Both the responses induced by IB-MECA were attenuated by treatment with U73122 or phorbol 12-myristate 13-acetate. 6. These data suggest the presence of both **A2B** and A3 **adenosine** receptors in mouse pineal tumour cells and that the **A2B** receptor is positively coupled to adenylyl cyclase whereas the A3 receptor is negatively coupled to adenylyl cyclase and also coupled to phospholipase C.

2/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11630915 21245186 PMID: 11347973
Selective **adenosine** A2A receptor antagonists.
Ongini E; Monopoli A; Cacciari B; Baraldi PG
Schering Plough Research Institute, San Raffaele Science Park, Milan, Italy.

Il Farmaco (Italy) Jan-Feb 2001, 56 (1-2) p87-90, ISSN 0014-827X
Journal Code: ACZ
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

In the early 1990s it became clear that the A2A **adenosine** receptor had characteristics that made it distinct from the other A1, **A2B** and A3 **adenosine** receptors. Great progress has been made with the discovery of selective A2A receptor antagonists. A variety of synthetic substitutions on the xanthine moiety led the chemists of Kyowa-Hakko to discover that introduction of the styryl group in the 8 position of xanthines was critical in achieving compounds endowed with selective A2A receptor antagonistic properties. One compound, KW 6002, (E)1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methylxanthine, is currently being developed for treatment of Parkinson's disease. A number of non-xanthine heterocycles have also been synthesized starting from the non-selective **adenosine antagonist** CGS 15943, a triazoloquinazoline. Thus, replacement of the phenyl ring of CGS 15943 with a heterocyclic ring such as pyrazole or imidazole, led to a series of interesting compounds whose prototype, SCH 58261, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine, has become a reference A2A receptor **antagonist**. Modification of N7 substituents has progressed to optimize A2A receptor selectivity and pharmacokinetic characteristics. A related class of compounds having a bicyclic instead of the tricyclic ring structure is also of interest. The prototype of these triazintriazolo derivatives, ZM 241385, is a potent A2A receptor **antagonist**; however, it also shows interactions with **A2B** receptors. The relevance of the A2A receptors in specific disease states, especially in the central nervous system, makes this class of **adenosine** receptor blockers of interest for treatment of neurodegenerative disorders such as Parkinson's disease.

2/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11571709 21198710 PMID: 11303729

Adenosine inhibits neutrophil vascular endothelial growth factor release and transendothelial migration via **A2B** receptor activation.

Wakai A; Wang JH; Winter DC; Street JT; O'Sullivan RG; Redmond HP

Department of Academic Surgery, Cork University Hospital, Cork, Republic of Ireland.

Shock (United States) Apr 2001, 15 (4) p297-301, ISSN 1073-2322
Journal Code: CAE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The effects of **adenosine** on neutrophil (polymorphonuclear neutrophils: PMN)-directed changes in vascular permeability are poorly characterized. This study investigated whether **adenosine** modulates activated PMN vascular endothelial growth factor (vascular permeability factor: VEGF) release and transendothelial migration. PMN activated with tumour necrosis factor-alpha (TNF-alpha, 10 ng/mL) were incubated with **adenosine** and its receptor-specific analogues. Culture supernatants were assayed for VEGF. PMN transendothelial migration across human umbilical vein endothelial cell (HUVEC) monolayers was assessed in vitro. Adhesion molecule receptor expression was assessed flow cytometrically. **Adenosine** and some of its receptor-specific analogues dose-dependently inhibited activated PMN VEGF release. The rank order of potency was consistent with the affinity profile of human **A2B** receptors. The inhibitory effect of **adenosine** was reversed by 3,7-dimethyl-1-propargylxanthine, an A2 receptor **antagonist**. **Adenosine** (100 microM) or the **A2B** receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA, 100 microM) significantly reduced PMN transendothelial migration. However, expression of activated PMN beta2 integrins and HUVEC ICAM-1 were not significantly altered by

adenosine or NECA. **Adenosine** attenuates human PMN VEGF release and transendothelial migration via the **A2B** receptor. This provides a novel target for the modulation of PMN-directed vascular hyperpermeability in conditions such as the capillary leak syndrome.

2/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11562662 21400870 PMID: 11509639
Methotrexate suppresses nf-kappab activation through inhibition of ikappabalpha phosphorylation and degradation.
Majumdar S; Aggarwal BB
Cytokine Research Laboratory, Department of Bioimmunotherapy, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030.
Journal of immunology (United States) Sep 1 2001, 167 (5) p2911-20, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
Methotrexate (MTX), a folate **antagonist**, is a commonly used anti-inflammatory, antiproliferative, and immunosuppressive drug whose mode of action is not fully established. Due to the central role of NF-kappaB in these responses, we postulated that MTX must mediate its effects through suppression of NF-kappaB activation. We investigated the effects of MTX on NF-kappaB activation induced by TNF in Jurkat cells. The treatment of these cells with MTX suppressed TNF-induced NF-kappaB activation with optimum effects occurring at 10 &mgr;M MTX for 60 min. These effects were not restricted to Jurkat cells because other cell types were also inhibited. Besides TNF, MTX also suppressed the NF-kappaB activation induced by various other inflammatory stimuli. The suppression of TNF-induced NF-kappaB activation by MTX correlated with inhibition of IkappaBalpha degradation, suppression of IkappaBalpha phosphorylation, abrogation of IkappaBalpha kinase activation, and inhibition of NF-kappaB-dependent reporter gene expression. Because ecto 5' nucleotidase inhibitor (alpha,beta-methylene **adenosine**-5'-diphosphate) blocked the effect of MTX, **adenosine** mimicked the effect of MTX, and **adenosine** **A2b** receptor **antagonist** (3,7-dimethyl-1-propargylxanthine) reversed the inhibitory effect of MTX, we suggest that MTX suppresses NF-kappaB activation by releasing **adenosine**. A partial reversal of MTX-induced NF-kappaB suppression by thymidine and folinic acid indicates the role of the thymidylate synthase pathway also. Overall, our results clearly demonstrate that MTX suppresses NF-kappaB activation through the release of **adenosine**, which may contribute to the role of MTX in anti-inflammatory, immunomodulatory, and antiproliferative effects.

2/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11283095 21196395 PMID: 11299238
Receptor subtypes mediating **adenosine**-induced dilation of cerebral arterioles.
Ngai AC; Coyne EF; Meno JR; West GA; Winn HR
Department of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington 98104, USA. ngai@u.washington.edu
American journal of physiology (United States) May 2001, 280 (5) pH2329-35, ISSN 0363-6135 Journal Code: DKM
Contract/Grant No.: NS-21076, NS, NINDS; NS-30305, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The purpose of this study was to investigate the receptor subtypes that mediate the dilation of rat intracerebral arterioles elicited by **adenosine**. Penetrating arterioles were isolated from the rat brain,

cannulated with the use of a micropipette system, and luminally pressurized to 60 mmHg. Both **adenosine** and the A2A receptor-selective agonist CGS-21680 induced dose-dependent vasodilation (-logEC(50): 6.5 +/- 0.2 and 8.6 +/- 0.3, respectively). However, **adenosine**, which is capable of activating both A2A and **A2B** receptors, caused a greater maximal dilation than CGS-21680. The A2A receptor-selective **antagonist** ZM-241385 (0.1 microM) only partially inhibited the dilation induced by **adenosine** but almost completely blocked CGS-21680-induced dilation. Neither 8-cyclopentyl-1,3-dipropylxanthine (0.1 microM), an A1 receptor-selective **antagonist**, nor MRS-1191 (0.1 microM), an A3 receptor-selective **antagonist**, attenuated **adenosine** dose responses. Moreover, ZM-241385 had no effect on the dilation induced by ATP (10 microM) or acidic (pH 6.8) buffer. We concluded that the A2A receptor subtype mediates **adenosine** -induced dilation of intracerebral arterioles in the rat brain. Furthermore, our results suggest that **A2B** receptors may also participate in the dilation response to **adenosine**.

2/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11281051 21155461 PMID: 11230251
A(2B) receptors mediate the antimitogenic effects of **adenosine** in cardiac fibroblasts.
Dubey RK; Gillespie DG; Zacharia LC; Mi Z; Jackson EK
Center for Clinical Pharmacology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA. raghvendra.dubey@fhk.usz.ch
Hypertension (United States) Feb 2001, 37 (2) p716-21, ISSN 1524-4563 Journal Code: DCZ
Contract/Grant No.: HL-35909, HL, NHLBI; HL-55314, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine inhibits growth of cardiac fibroblasts; however, the **adenosine** receptor subtype that mediates this antimitogenic effect remains undefined. Therefore, the goals of this study were to determine which **adenosine** receptor subtype mediates the antimitogenic effects of **adenosine** and to investigate the signal transduction mechanisms involved. In rat left ventricular cardiac fibroblasts, PDGF-BB (25 ng/mL) stimulated DNA synthesis ((3)H-thymidine incorporation), cellular proliferation (cell number), collagen synthesis ((3)H-proline incorporation), and MAP kinase activity. The **adenosine** receptor agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N(6)-cyclopentyladenosine, 4-aminobenzyl-5'-N-methylcarboxamidoadenosine, or CGS-21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an A(2B) receptor-mediated effect. The **adenosine** receptor antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an **antagonist** profile consistent with an A(2) receptor-mediated effect. Antisense, but not sense or scrambled, oligonucleotides to the A(2B) receptor stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and collagen synthesis. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of **adenosine** deaminase and **adenosine** kinase, respectively) were abolished by antisense, but not scrambled or sense, oligonucleotides to the A(2B) receptor. Our findings strongly support the hypothesis that **adenosine** causes inhibition of CF growth by activating A(2B) receptors coupled to inhibition of MAP kinase activity. Thus, A(2B) receptors may play a critical role in regulating cardiac remodeling associated with CF proliferation. Pharmacologic or molecular biological activation of A(2B) receptors may prevent cardiac remodeling associated

with hypertension, myocardial infarction, and myocardial reperfusion injury after ischemia.

2/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11203405 21167351 PMID: 11266650
3H]MRS 1754, a selective **antagonist** radioligand for A(2B) **adenosine** receptors.
Ji X; Kim YC; Ahern DG; Linden J; Jacobson KA
Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bldg. 8A, Room B1A-19, Bethesda, MD 20892, USA.
Biochemical pharmacology (England) Mar 15 2001, 61 (6) p657-63, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
MRS 1754 [N-(4-cyanophenyl)-2-[4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3-dipropyl-1H-purin-8-yl)-phenoxy]acetamide] is a selective **antagonist** ligand of A(2B) **adenosine** receptors. This is the least well-defined **adenosine** receptor subtype, and A(2B) antagonists have potential as antiasthmatic drugs. For use as a radioligand, MRS 1754, a p-cyanoanilide xanthine derivative, was tritiated on the propyl groups in a two-step reaction using a p-carboxamido precursor, which was dehydrated to the cyano species using trifluoroacetic anhydride. [3H]MRS 1754 (150 Ci/mmol) bound to recombinant human A(2B) **adenosine** receptors in membranes of stably transfected HEK-293 cells. Specific binding was saturable, competitive, and followed a one-site model, with a K(D) value of 1.13 +/- 0.12 nM and a B(max) value of 10.9 +/- 0.6 pmol/mg protein. Specific binding utilizing 0.7 nM [3H]MRS 1754 was > 70% of total binding. The affinity calculated from association and dissociation binding constants was 1.22 nM (N = 4). Binding to membranes expressing rat and human A(1) and A(3) **adenosine** receptors was not significant, and binding in membranes of HEK-293 cells expressing human A(2A) receptors was of low affinity (K(D) > 50 nM). The effects of cations and chelators were explored. Specific binding was constant over a pH range of 4.5 to 6.5, with reduced binding at higher pH. The pharmacological profile in competition experiments with [3H]MRS 1754 was consistent with the structure-activity relationship for agonists and antagonists at A(2B) receptors. The K(i) values of XAC (xanthine amine congener) and CPX (8-cyclopentyl-1,3-dipropylxanthine) were 16 and 55 nM, respectively. NECA (5'-N-ethylcarboxamidoadenosine) competed for [3H]MRS 1754 binding with a K(i) of 570 nM, similar to its potency in functional assays. Thus, [3H]MRS 1754 is suitable as a selective, high-affinity radioligand for A(2B) receptors.

2/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11139074 21094552 PMID: 11159049
Regulation of G protein-coupled receptor-adenylyl cyclase responsiveness in human airway smooth muscle by exogenous and autocrine **adenosine**.
Mundell SJ; Olah ME; Panettieri RA; Benovic JL; Penn RB
Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, 233 S. 10th St., Philadelphia, PA 19107, USA.
American journal of respiratory cell and molecular biology (United States) Feb 2001, 24 (2) p155-63, ISSN 1044-1549 Journal Code: AOB
Contract/Grant No.: HL58506, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine is a mediator of bronchoconstriction in asthmatics and is believed to mediate its effects through **adenosine** receptor activation

in inflammatory cells. In this study, we identify human airway smooth muscle (ASM) as a direct target of **adenosine**. Acute exposure of human ASM cultures to **adenosine** receptor (AR) agonists resulted in rapid accumulation of cyclic **adenosine** monophosphate (cAMP) with a pharmacologic profile consistent with A(2b)AR activation. Little or no evidence of A1AR or A3AR expression was suggested on acute addition of various AR ligands, although a low level of A1ARs was identified in radioligand binding studies. Treatment with **adenosine** deaminase suggested that human ASM cultures secrete **adenosine** that feeds back on A(2b)ARs and regulates basal cAMP levels as well as a small degree of A(2b)AR, beta(2)AR, and prostaglandin E(2) receptor desensitization. When subjected to chronic treatment with AR agonists or agents that enhance accumulation of endogenous, extracellular **adenosine**, a dual effect of A(2b)AR desensitization and adenylyl cyclase (AC) sensitization was observed. This AC sensitization was eliminated by pertussis toxin and partially reversed by the A1AR **antagonist** 8-cyclopentyl-1,3-dipropylxanthine, suggesting a contributory role for the A1AR. Overexpression of A1ARs and A(2b)ARs in human ASM cultures resulted in differential effects on basal, agonist-, and AC-mediated cAMP production. These data demonstrate that human ASM is a direct target of exogenous and autocrine **adenosine**, with effects determined by differential contributions of A(2b) and A1 **adenosine** receptors that are time-dependent. Accordingly, the relative distribution and activation of AR subtypes in ASM in vivo may influence airway function in diseases such as asthma and warrant consideration in therapeutic strategies that target ARs or alter nucleotide/nucleoside levels in the airway.

2/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11002621 21103886 PMID: 11158259
Beta,gamma-methylene ATP-induced cAMP formation in C6Bu-1 cells: involvement of local metabolism and subsequent stimulation of **adenosine A2B** receptor.
Ohkubo S; Kumazawa K; Sagawa K; Kimura J; Matsuoka I
Department of Pharmacology, School of Medicine, Fukushima Medical University, Fukushima, Japan.
Journal of neurochemistry (United States) Feb 2001, 76 (3) p872-80, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The mechanism underlying beta,gamma-methylene ATP (beta,gamma-MeATP)-induced cAMP elevation was investigated in rat glioma C6Bu-1 cells. Beta,gamma-MeATP increased forskolin-stimulated cAMP formation in a manner sensitive to both the P1 **antagonist** xanthine amine congener (XAC) and the P2 **antagonist** pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid (PPADS). **Adenosine** deaminase (ADA; 1 U/mL), which abolished the **adenosine**-induced response, did not eliminate the beta,gamma-MeATP-induced response. However, combination of ADA with alpha,beta-methylene ADP (alpha,beta-MeADP), an ecto-5'-nucleotidase inhibitor, blocked the beta,gamma-MeATP-induced response. AMP, the substrate for ecto-5'-nucleotidase, also induced cAMP formation in a manner sensitive to XAC and alpha,beta-MeADP inhibition. However, the AMP-induced response was not blocked by PPADS. HPLC analyses revealed that **adenosine** was generated from beta,gamma-MeATP and AMP. In addition, alpha,beta-MeADP inhibited the conversion of beta,gamma-MeATP and AMP to **adenosine**, whereas PPADS blocked **adenosine** formation from beta,gamma-MeATP but not from AMP. [3H]**Adenosine** generated from [3H]AMP was preserved on the cell surface environment even in the presence of ADA. The mRNAs for ecto-phosphodiesterase/pyrophosphatase 1 (EC 3.1.4.1), ecto-5'-nucleotidase (EC 3.1.3.5) and **adenosine A2B** receptor were detected by RT-PCR. These results suggest that C6Bu-1 cells possess ecto-enzymes converting beta,gamma-MeATP to **adenosine**, and

the locally accumulated **adenosine** in this mechanism efficiently stimulates **A2B** receptors in a manner resistant to exogenous ADA.

2/3,Ab/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10922906 20574584 PMID: 11125027
A3 **adenosine** receptor activation triggers phosphorylation of protein kinase B and protects rat basophilic leukemia 2H3 mast cells from apoptosis.
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Department of Cardiovascular Medicine, University of Virginia, Charlottesville, Virginia 22908-0466, USA.
Molecular pharmacology (UNITED STATES) Jan 2001, 59 (1) p76-82, ISSN 0026-895X Journal Code: NGR
Contract/Grant No.: R01-HL37942, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine accumulates to high levels in inflamed or ischemic tissues and activates A3 **adenosine** receptors (ARs) on mast cells to trigger degranulation. Here we show that stimulation of rat basophilic leukemia (RBL)-2H3 mast-like cells with the A3 AR agonists N6-(3-iodobenzyl-5'-N-methylcarboxamidoadenosine (IB-MECA; 10 nM) or inosine (1 microM) stimulates phosphorylation of protein kinase B (Akt). IB-MECA (1 microM) also causes a >50% reduction in apoptosis caused by exposure of RBL-2H3 cells to UV light. Akt phosphorylation is not stimulated by 100 nM N6-cyclopentyladenosine (A1-selective) or CGS21680 (A2A-selective) and is absent in cells pretreated with wortmannin or pertussis toxin. The KI values of the AR antagonists BW-1433 and 8-sulfophenyltheophylline (8-SPT) were determined in radioligand binding assays for all four subtypes of rat ARs: BW-1433 (A1, 5.8 +/- 1.0 nM; A2A, 240 +/- 37; **A2B**, 30 +/- 10; A3, 12,300 +/- 3, 700); 8-SPT (A1, 3.2 +/- 1.1 microM; A2A, 57 +/- 4; A2), 2.2 +/- 0.8; A3, >100). BW-1433 and the A3-selective **antagonist** MRS1523 (5 microM), but not 8-SPT (100 microM), block IB-MECA-induced protection from apoptosis, confirming the A3 AR as the mediator of the antiapoptotic response. The data suggest that **adenosine** and inosine activate Gi-coupled A3 ARs to protect mast cells from apoptosis by a pathway involving the betagamma subunits of Gi, phosphatidylinositol 3-kinase beta, and Akt. We speculate that activation of A3 ARs on mast cells or other cells that express A3 ARs (e.g., eosinophils) may facilitate their survival and accumulation in inflamed tissues.

2/3,Ab/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10799583 20050832 PMID: 10581320
Sensitization of visceral afferents to bradykinin in rat jejunum in vitro.
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Journal of physiology (ENGLAND) Dec 1 1999, 521 Pt 2 p517-27, ISSN 0022-3751 Journal Code: JQV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. We have investigated the effects of inflammatory mediators on visceral afferent discharge and afferent responses to bradykinin (BK) in rat jejunum using a novel in vitro technique. 2. Prostaglandin E2 (1 microM) augmented responses to BK without affecting basal firing, while histamine (100 microM) and **adenosine** (100 microM) activated basal discharge and

enhanced BK responses. In contrast, 5-HT (100 microM) increased basal discharge without influencing responses to BK. 3. Afferent discharge induced by histamine was inhibited by both H1 (pyrilamine) and H3 (thioperamide) but not H2 (ranitidine) receptor antagonists at 10 microM. In contrast, sensitization to BK induced by histamine was inhibited by ranitidine (10 microM). 4. Afferent discharge induced by **adenosine** was blocked by the A1 receptor **antagonist** DPCPX (10 microM) but remained unaffected by A2A receptor blockade with ZM241385 (10 microM). In contrast, sensitization of BK responses by **adenosine** was unaffected by both antagonists. Basal discharge and BK-induced responses were unaffected by the A3 receptor agonist IB-MECA (1 microM). While involvement of **A2B** receptors is not excluded, **adenosine** may activate afferent discharge through A1 receptors, while sensitization to BK could involve a receptor other than A1, A2A or A3, possibly the **A2B** receptor. 5. Inhibition of cyclo-oxygenase with naproxen (10 microM) prevented sensitization after histamine but not **adenosine**. 6. Sensitization was mimicked by dibutyryl cAMP. This occurred without changes in basal firing and was unaffected by naproxen. 7. In conclusion, afferent discharge induced by BK is augmented by histamine, **adenosine** and PGE2, but not by 5-HT. Evidence suggests that sensitization involves separate mechanisms from afferent activation. Sensitization may be mediated by increases in cAMP following direct activation by mediators at the nerve terminal or through indirect pathways such as the release of prostaglandins.

2/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10767900 98158791 PMID: 9490823
Adenosine modulates hypoxia-induced responses in rat PC12 cells via the A2A receptor.
Kobayashi S; Conforti L; Pun RY; Millhorn DE
Department of Molecular and Cellular Physiology, University of Cincinnati, 231 Bethesda Avenue, PO Box 576, Cincinnati, OH 45267-576, USA. kobaya@email.uc.edu
Journal of physiology (ENGLAND) Apr 1 1998, 508 (Pt 1) p95-107, ISSN 0022-3751 Journal Code: JQV
Contract/Grant No.: HL 59945, HL, NHLBI; R37 HL 33831, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The present study was undertaken to determine the role of **adenosine** in mediating the cellular responses to hypoxia in rat phaeochromocytoma (PC12) cells, an oxygen-sensitive clonal cell line. 2. Reverse transcriptase polymerase chain reaction studies revealed that PC12 cells express **adenosine** deaminase (the first catalysing enzyme of **adenosine** degradation) and the A2A and **A2B adenosine** receptors, but not the A1 or A3 **adenosine** receptors. 3. Whole-cell current- and voltage-clamp experiments showed that **adenosine** attenuated the hypoxia-induced membrane depolarization. The hypoxia-induced suppression of the voltage-sensitive potassium current (IK(V)) was markedly reduced by **adenosine**. Furthermore, extracellularly applied **adenosine** increased the peak amplitudes of IK(V) in a concentration-dependent manner. This increase was blocked by pretreatment not only with a non-specific **adenosine** receptor **antagonist**, 8-phenyltheophylline (8-PT), but also with a selective A2A receptor **antagonist**, ZM241385. 4. Ca2+ imaging studies using fura-2 acetoxymethyl ester (fura-2 AM) revealed that the increase in intracellular free Ca2+ during hypoxic exposure was attenuated significantly by **adenosine**. Voltage-clamp studies showed that **adenosine** inhibited the voltage-dependent Ca2+ currents (ICa) in a concentration-dependent fashion. This inhibition was also abolished by both 8-PT and ZM241385. 5. The modulation of both IK(V) and ICa by **adenosine** was prevented by intracellular application of an inhibitor

of protein kinase A (PKA), PKA inhibitor fragment (6-22) amide. In addition, the effect of **adenosine** on either IK(V) or IC[redacted] was absent in PKA-deficient PC12 cells. 6. These results indicate that the modulatory effects of **adenosine** on the hypoxia-induced membrane responses of PC12 cells are likely to be mediated via activation of the A2A receptor, and that the PKA pathway is required for these modulatory actions. We propose that this modulation serves to regulate membrane excitability in PC12 cells and possibly other oxygen-sensitive cells during hypoxia.

2/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10734588 20437134 PMID: 10983840
Implication of **adenosine** A2A receptors in hypotension-induced vasodilation and cerebral blood flow autoregulation in rat pial arteries.
Shin HK; Park SN; Hong KW
Center for Biofunctional Molecule, Pohang University of Science and Technology, Korea.
Life sciences (ENGLAND) Aug 11 2000, 67 (12) p1435-45, ISSN 0024-3205 Journal Code: L62
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
This study aimed to evaluate the role for **adenosine** A2A receptors in the autoregulatory vasodilation to hypotension in relation with cerebral blood flow (CBF) autoregulation in rat pial arteries. Changes in pial artery diameters were observed directly through a closed cranial window. Vasodilation induced by **adenosine** was markedly suppressed by ZM 241385 (1 micromol/l, A2A **antagonist**) and alloxazine (1 micromol/l, **A2B antagonist**), but not by 8-cyclopentyltheophylline (CPT, 1 micromol/l, A1 **antagonist**). CGS-21680-induced vasodilation was more strongly inhibited by ZM 241385 (25.3-fold; P<0.05) than by alloxazine. In contrast, 5'-N-ethylcarboxamido-**adenosine** (NECA)-induced vasodilation was more prominently suppressed by alloxazine (12.0-fold; P<0.001) than by ZM 241385. The autoregulatory vasodilation in response to acute hypotension of the pial arteries was significantly suppressed by ZM 241385, but not by CPT and alloxazine. Consistent with this finding, the lower limit of CBF autoregulation significantly shifted to a higher blood pressure by 1 micromol/l of ZM 241385 (53.0+/-3.9 mm Hg to 69.2+/-2.9 mm Hg, P<0.01) and 10 micromol/l of glibenclamide (54.7+/-6.5 mm Hg to 77.9+/-4.2 mm Hg, P<0.001), but not by CPT and alloxazine. Thus, it is suggested that **adenosine**-induced vasodilation of the rat pial artery is mediated via activation of **adenosine** A2A and **A2B** receptors, but not by A1 subtype, and activation of **adenosine** A2A receptor preferentially contributes to the autoregulatory vasodilation via activation of ATP-sensitive K+ channels in response to hypotension and maintenance of CBF autoregulation.

2/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10725626 20355140 PMID: 10896720
Adenosine inhibits voltage-dependent Ca2+ currents in rat dissociated supraoptic neurones via A1 receptors.
Noguchi J; Yamashita H
Department of Physiology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu 807-8555, Japan. n-jun@med.uoeh-u.ac.jp
Journal of physiology (ENGLAND) Jul 15 2000, 526 Pt 2 p313-26, ISSN 0022-3751 Journal Code: JQV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

1. The modulation of voltage-dependent Ca2+ currents (ICa) by **adenosine** was investigated in magnocellular neurons acutely dissociated from the rat hypothalamic supraoptic nucleus (SON) by using the whole-cell patch-clamp technique. 2. **Adenosine** dose dependently and reversibly inhibited ICa elicited by depolarizing voltage steps from a holding potential of -80 mV to potentials ranging from -30 to +20 mV. The mean (+ - s.e.m.) maximum inhibition rate was 36.1 +/- 4.1 % (n = 6) at -20 mV and the EC50 was 9.8 x 10-7 M (n = 6). 3. The inhibition of ICa by **adenosine** was completely reversed by the selective A1 receptor **antagonist** 8-cyclopentyl theophylline (CPT), and was mimicked by the selective A1 receptor agonist N 6-cyclohexyladenosine (CHA). 4. The inhibition by CHA was strongly reduced when ICa was inhibited by omega-conotoxin GVIA, a blocker of N-type Ca2+ channels. 5. The **adenosine** -induced inhibition of ICa was largely reversed by a depolarizing prepulse to +150 mV for 100 ms, which is known to reverse the inhibition of Ca2+ channels mediated by G-protein betagamma subunits. 6. The **adenosine** receptor-mediated inhibition of ICa was not abolished by intracellularly applied preactivated pertussis toxin (PTX). 7. Using immunohistochemistry, Gzalpha-like immunoreactivity (a PTX-resistant inhibitory G-protein) was observed throughout the SON. 8. These results suggest that **adenosine** modulates the neuronal activity of SON neurones by inhibiting N-type voltage-dependent Ca2+ channels via A1 receptors which are coupled to PTX-resistant G-proteins.

2/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10714811 20382923 PMID: 10924064

Adenosine A(2A) and A(2B) receptors in cultured human and porcine coronary artery endothelial cells.

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American journal of physiology (UNITED STATES) Aug 2000, 279 (2) pH650-6, ISSN 0363-6135 Journal Code: DKM

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Languages: ENGLISH

Document type: Journal Article

Record type: Completed

We investigated the role of the cAMP link to the signal transduction mechanism coupled with **adenosine** A(2A) and A(2B) receptors in cultured human coronary artery endothelial cells (HCAEC) and porcine coronary artery endothelial cells (PCAEC). 2-[4-[2-2-[(4-aminophenyl)methylcarbonylamino]ethylaminocarbon yl eth yl]phenyl]eth ylamino-5'- ethylcarboxamidoadenosine ((125)I-PAPA-APEC) (PAPA-APEC) was used to demonstrate the specific binding in PCAEC membranes. The specific binding was saturable and reversible with a maximal number of binding sites (B(max) of 240 fmol/mg protein, and scatchard analysis revealed a single class of binding site with an equilibrium dissociation constant (K(d)) of 1. 17 + - 0.035 nM. In competition experiments, **adenosine** receptor agonists showed the following order of potency (based on IC(50)): 5'-(N-ethylcarboxamido)**adenosine** (NECA) >/= CGS-21680 > 2-chloroadenosine. This order appears to be consistent with the A(2) **adenosine** receptor classification. We also studied the effects of **adenosine** agonists on the accumulation of cAMP as an indirect approach to show the presence of functional A(2) receptors. Similarly, the same **adenosine** agonists (10(-7)-10(-4) M) elicited the production of cAMP in intact endothelial cells in a dose-dependent manner, exhibiting consistently with the A(2) **adenosine** receptor classification. A selective A(2A) **adenosine** receptor **antagonist** (ZM-241385, 10(-8) M) significantly inhibited the effect of CGS-21680 on cAMP but only partly inhibited the effect of NECA, suggesting the presence of both A(2A) and A(2B) receptors. Western blot analysis further showed the immunoreactivity of A(2A) and A(2B) receptor at 45 and 36 kDa,

respectively, in both HCAEC and PCAEC. Direct evidence for the presence of A(2A) and A(2B) receptors in cultured HCAEC and PCAEC by reverse transcription-polymerase chain reaction (RT-PCR), revealed expected PCR product sizes (205 and 173 bp) for A(2A) and A(2B) receptors in HCAEC and PCAEC, respectively. The data show that adenylate cyclase-coupled **adenosine** A(2A) and A(2B) receptors are present in coronary endothelial cells.

2/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10699610 20385322 PMID: 10926550
Gene expression and function of **adenosine** A(2A) receptor in the rat carotid body.
Kobayashi S; Conforti L; Millhorn DE
Department of Molecular and Cellular Physiology, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio 45267-0576, USA.
American journal of physiology (UNITED STATES) Aug 2000, 279 (2) pL273-82, ISSN 1040-0605 Journal Code: DKO
Contract/Grant No.: HL-59945, HL, NHLBI; R37-HL-33831, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The present study was undertaken to determine whether rat carotid bodies express **adenosine** (Ado) A(2A) receptors and whether this receptor is involved in the cellular response to hypoxia. Our results demonstrate that rat carotid bodies express the A(2A) and A(2B) Ado receptor mRNAs but not the A(1) or A(3) receptor mRNAs as determined by reverse transcriptase-polymerase chain reaction. In situ hybridization confirmed the expression of the A(2A) receptor mRNA. Immunohistochemical studies further showed that the A(2A) receptor is expressed in the carotid body and that it is colocalized with tyrosine hydroxylase in type I cells. Whole cell voltage-clamp studies using isolated type I cells showed that Ado inhibited the voltage-dependent Ca(2+) currents and that this inhibition was abolished by the selective A(2A) receptor **antagonist** ZM-241385. Ca(2+) imaging studies using fura 2 revealed that exposure to severe hypoxia induced elevation of intracellular Ca(2+) concentration ([Ca(2+)](i)) in type I cells and that extracellularly applied Ado significantly attenuated the hypoxia-induced elevation of [Ca(2+)](i). Taken together, our findings indicate that A(2A) receptors are present in type I cells and that activation of A(2A) receptors modulates Ca(2+) accumulation during hypoxia. This mechanism may play a role in regulating intracellular Ca(2+) homeostasis and cellular excitability during hypoxia.

2/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10674723 20090779 PMID: 10625308
Extracellular **adenosine** induces apoptosis of human arterial smooth muscle cells via A(2b) purinoceptor.
Peyot ML; Gadeau AP; Dandre F; Belloc I; Dupuch F; Desgranges C
Unite INSERM 441, Pessac, France.
Circulation research (UNITED STATES) Jan 7-21 2000, 86 (1) p76-85, ISSN 0009-7330 Journal Code: DAJ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Apoptosis of arterial smooth muscle cells (ASMCs) could play an important role in the pathogenesis of atherosclerosis and restenosis. Recent studies have demonstrated that extracellular **adenosine** induces apoptosis in various cell types. Our aim was to delineate the capacity of this nucleoside to induce ASMC apoptosis in arterial diseases. We demonstrate that **adenosine** dose-dependently triggers apoptosis of cultured human

ASMCs. Apoptotic cell death was quantified by analysis of nuclear chromatin morphology and characterized by DNA laddering. The involvement of **adenosine** receptors was suggested, because neither an **adenosine** deaminase inhibitor, erythro-9-(2-hydroxy-3-nonyl) adenine hydrochloride, nor an inhibitor of cellular nucleoside transport, dipyridamole, was able to inhibit **adenosine** -induced ASMC apoptosis. In contrast, an A(1)/A(2)-**adenosine** receptor **antagonist** , xanthine amine congener, totally inhibited **adenosine**-induced apoptosis. Furthermore, among more selective inhibitors of P(1) purinoceptor subtypes, only alloxazine, an **antagonist** of A(1)- and A(2)-**adenosine** receptors, completely inhibited **adenosine**-induced ASMC apoptosis, suggesting that **adenosine** triggers ASMC apoptosis via either 1 or both of these receptors. However, 8-cyclopentyl-1,3-dipropylxanthine, 8-(3-chlorostyryl) caffeine, and 3-ethyl-5-benzyl-2-methyl-4-phenylethynyl-6-phenyl-1, 4-(+/-)-dihydropyridine-3,5-dicarboxylate, which are A(1)-, A(2a)-, and A(3)-**adenosine** receptor antagonists, did not inhibit **adenosine** -induced apoptosis, suggesting an involvement of the A(2b)-receptor in this process. Moreover, the cAMP increase followed by cAMP-dependent protein kinase activation appears essential to mediate **adenosine** -induced ASMC apoptosis, thus confirming the previous hypothesis. These results indicate that **adenosine**-induced apoptosis of ASMCs is essentially mediated via A(2b)-**adenosine** receptor and involves a cAMP-dependent pathway.

2/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10579710 20191635 PMID: 10725262

The role of **adenosine** receptors in the action of theophylline on human peripheral blood mononuclear cells from healthy and asthmatic subjects.

Landells LJ; Jensen MW; Orr LM; Spina D; O'Connor BJ; Page CP

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British journal of pharmacology (ENGLAND) Mar 2000, 129 (6) p1140-4, ISSN 0007-1188 Journal Code: B00

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

1. The aim of the present study was to investigate the role of **adenosine A2b** receptors in the anti-proliferative action of theophylline in human peripheral blood mononuclear cells (HPBMC) from healthy and asthmatic subjects. 2. Theophylline significantly inhibited PHA-induced proliferation of HPBMC from both healthy and asthmatic donors but only at relatively high concentrations at 1 mM ($P<0.05$). Enprophylline, a drug which also acts as a non-selective phosphodiesterase (PDE) inhibitor and is a selective **A2b** receptor **antagonist**, had no significant effect on proliferation of cells from either group at concentrations up to 10 microM ($P>0.05$; n=6). 3. **Adenosine** deaminase (2 u ml(-1)), which metabolizes **adenosine**, had no significant effect on PHA-induced HPBMC proliferation over a range of concentrations (0 - 8 microg ml(-1)) in cells from either healthy or asthmatic subjects. 4. The **adenosine** receptor agonists N(6)-cyclopentyladenosine (CPA, A1-selective) and 5'-N-ethylcarboxamidoadenosine (NECA, A1/A2) produced a small but significant inhibition of PHA-induced proliferation of HPBMC from healthy and asthmatic subjects (10 microM, $P<0.05$; n=6). In contrast, 5'-N-ethylcarboxamido-2-[4-(2-]carboxyethyl)phenethyl]**adenosine** (CGS2 1680, A2a-selective) was without significant effect ($P>0.05$; n=6). 5. The **adenosine** receptor **antagonist** alloxazine (**A2b**-selective) had no significant effect, while 8(3-chlorostyryl)caffeine,(CSC, A2a-selective) significantly inhibited PHA-induced proliferation of HPBMC from both groups ($P<0.05$; n=6). 6. Our results suggest that endogenous or exogenous **adenosine** has little effect on the proliferation of HPBMC

obtained from healthy or asthmatic subjects. Thus it would appear that the effect of high concentrations of theophylline is not related to **adenosine** receptor antagonism.

2/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10563811 20160572 PMID: 10696084
Molecular identification and pharmacological characterization of **adenosine** receptors in the guinea-pig colon.
Kadowaki M; Takeda M; Tokita K; Hanaoka K; Tomoi M
Pharmacological Research Laboratory, Fujisawa Pharmaceutical Co. Ltd., Osaka 532-0031, Japan.
British journal of pharmacology (ENGLAND) Mar 2000, 129 (5) p871-6, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The aim of this study is to elucidate the role of **adenosine** in the motor function of the guinea-pig distal colon.2 To determine whether **adenosine** A(1) receptors and A(2B) receptors are expressed in the guinea-pig colon, we employed the reverse transcription-polymerase chain reaction (RT - PCR). The gene expression of A(1) receptor and A(2B) receptor was found for the first time in the guinea-pig proximal and distal colon.3 **Adenosine** A(1) agonist N(6)-cyclopentyladenosine (CPA), and A(1)/A(2) agonist 5'-N-ethylcarboxamidoadenosine (NECA) concentration-dependently inhibited neurogenic responses to electrical field stimulation (EC(50)=1.0[illegible]x10(-8) and 2.12x10(-8) M) in the longitudinal muscle, but A(2A) agonist 2-p-(2-carboxyethyl)phenylethylamino-5'-N-ethycarboxamido-adenosine (CGS21680) had only a slight inhibitory effect (25.9%, 1 microM). A(1) **antagonist** 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 10 nM: A(1) selective concentration) antagonized responses to CPA and NECA. Furthermore, the affinity order of antagonists at inhibiting the effect NECA was: DPCPX>8-phenyltheophylline (8-PT: A(1)/A(2) **antagonist**).3 In the presence of tetrodotoxin (TTX, 0.3 microM), CPA and NECA relaxed myogenic precontraction induced by KCl (50 mM) (EC(50)=1.26x10(-5) and 1.04x10(-5) M, respectively), but CGS21680 (1 microM) did not cause any relaxation. DPCPX did not affect responses to CPA and NECA at a concentration of 10 nM, but a higher concentration (1 microM) of DPCPX and 10 microM of 8-PT antagonized those responses.5 These data lead us to the hypothesis that **adenosine** may mediate relaxation through two different inhibitory receptor subtypes; A(1) receptors on the enteric neuron and A(2B) receptor on the smooth muscle in the guinea-pig distal colon.

2/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10554807 20158770 PMID: 10694229
Adenosine induces cyclic-AMP formation and inhibits endothelin-1 production/secretion in guinea-pig tracheal epithelial cells through A(2B) **adenosine** receptors.
Pelletier S; Dube J; Villeneuve A; Gobeil F; Bernier SG; Battistini B; Guillemette G; Sirois P
Institut de Pharmacologie de Sherbrooke, Faculte de Medecine, Universite de Sherbrooke, Sherbrooke (PQ) Canada.
British journal of pharmacology (ENGLAND) Jan 2000, 129 (2) p243-50, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The **adenosine** receptor subtype mediating **adenosine** 3' : 5'-cyclic monophosphate (cyclic AMP) formation and the effect of its

activation on endothelin-1 (ET-1) secretion were studied in primary cultures of tracheal epithelial cells. 2. **Adenosine** analogues showed the following rank order of potency (pD(2) value) and intrinsic activity on the generation of cyclic AMP by tracheal epithelial cells: 5'-N-ethylcarboxyamidoadenosine (NECA, A(1)/A(2A)/A(2B), pD(2): 5.44+/-0.16)>**adenosine** (ADO, non selective, pD(2): 4.99+/-0. 09; 71+/-9% of NECA response) >/=2-Cl-**adenosine** (2CADO, non selective, pD(2): 4.72+/-0.14; 65+/-9% of NECA response)>>>CGS21680 (A(2A); inactive at up to 100 microM). 3. Cyclic AMP formation stimulated by NECA in guinea-pig tracheal epithelial cells was inhibited by **adenosine** receptor **antagonist** with the following order of apparent affinity (pA(2) value): Xanthine amine congeners (XAC, A(2A)/A(2B), 7.89+/-0.22)>CGS15943 (A(2A)/A(2B), 7.24+/-0. 26)>ZM241385 (A(2A), 6.64+/-0.14)>DPCPX (A(1), 6.51+/-0. 14)>3n-propylxanthine (weak A(2B), 4.30+/-0.18). This rank order of potency is typical for A(2B)-**adenosine** receptor. 4. **Adenosine** decreased basal and LPS-stimulated irET production in a concentration-dependent manner. Moreover, NECA but not CGS21680 inhibited LPS-induced irET production. 5. The inhibitory effect of NECA on LPS-induced irET production was reversed by XAC (pA(2)=8.84+/-0. 12) and DPCPX (pA(2)=8.10+/-0.22). 6. These results suggested that **adenosine** increased cyclic AMP formation and inhibited irET production/secretion by guinea-pig tracheal epithelial cells through the activation of a functional **adenosine** receptor that is most likely the A(2B) subtype. This **adenosine** receptor may be involved in the regulation of the level of ET-1 production/secretion by guinea-pig tracheal epithelial cells in physiological as well as in pathophysiological conditions.

2/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10492094 20131130 PMID: 10666062
Role of **adenosine** A(2B) receptors in vasodilation of rat pial artery and cerebral blood flow autoregulation.
Shin HK; Shin YW; Hong KW
Department of Pharmacology, College of Medicine, Pusan National University, Pusan 602-739, Korea.
American journal of physiology (UNITED STATES) Feb 2000, 278 (2) pH339-44, ISSN 0363-6135 Journal Code: DKM
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
This study was aimed to investigate the underlying mechanism of vasodilation induced by the activation of A(2B) **adenosine** receptors in relation to cerebral blood flow (CBF) autoregulation. Changes in pial arterial diameters were observed directly through a closed cranial window. N(omega)-nitro-L-arginine methyl ester (L-NAME, nitric oxide synthase inhibitor) significantly suppressed the concentration-dependent vasodilations induced by **adenosine** and 5'-N-ethylcarboxamido-**adenosine** (NECA) but not the vasodilation by CGS-21680 (A(2A)-receptor agonist). Moreover, NECA-induced vasodilation was suppressed by alloxazine (1 micromol/l) but not by ZM-241385 (1 micromol/l, A(2A) **antagonist**), which suggests mediation by A(2B)- receptor activation. Otherwise, the level of nitrite/nitrate was concentration dependently increased in the artificial cerebrospinal fluid (CSF) when **adenosine** and NECA were suffused over the cortical surface. L-NAME and alloxazine, but not ZM-241385, largely inhibited their releases. The lower limit of CBF autoregulation was little affected following pretreatment with L-NAME or alloxazine. Thus it is suggested that **adenosine**-induced vasodilation via activation of A(2B)-**adenosine** receptors of the rat pial artery is coupled to the production of nitric oxide, which contributes little to CBF autoregulation.

2/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10439232 20089693 PMID: 10624567
Use of the triazolotriazine [3H]ZM 241385 as a radioligand at recombinant human **A2B adenosine** receptors.
Ji XD; Jacobson KA
Molecular Recognition Section, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.
Drug design and discovery (SWITZERLAND) Nov 1999, 16 (3) p217-26, ISSN 1055-9612 Journal Code: A5B
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Radiolabeled ZM 241385 (4-(2-[7-amino-2- furyl 1,2,4 triazolo 2,3-a 1,3,5 triazin-5-ylaminoethyl)p henol), has previously been used as a high affinity radioligand for the labeling of A2A **adenosine** receptors in cell membranes. Another subtype, the **A2B** receptor, is the least well-defined subtype of **adenosine** receptors and lacks selective pharmacological probes. In the present study, we have used [3H]ZM 241385 as a radioligand to label recombinant human **A2B adenosine** receptors in HEK-293 cell membranes, that do not express A2A **adenosine** receptors, and found that the pharmacological profile is consistent with the SAR of **A2B** receptors. Saturable, specific binding (Kd 33.6 nM, Bmax 4.48 pmol/mg protein) that was best described by a one-site model was found, and specific binding was approximately 75% of total binding. [3H]ZM 241385 binding was displaceable by a large number of compounds known to interact with **A2B** receptors; thus, this method has promise as a tool in the search for agonists and antagonists selective for this subtype. Xanthine analogs, which are antagonists, proved to be the most potent displacers. The Ki of XAC, xanthine amine congener, was 12.3 nM, while CPX (8-cyclopentyl-1,3-dipropylxanthine) was less potent. The non-selective triazoloquinazoline **antagonist** CGS 15943 (Ki 16.4 nM), which is similar in structure to ZM 241385, was slightly less potent than XAC. The non-xanthine **A2B-antagonist** alloxazine displaced [3H]ZM 241385-binding with a Ki of 462 nM, similar to its affinity in functional assays. **Adenosine** derivatives known to activate this receptor subtype, such as NECA (5'-N-ethylcarboxamidoadenosine) and R-PIA (N6-phenylisopropyladenosine), were considerably less potent than the 8-substituted xanthines examined.

2/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10344186 99426953 PMID: 10496952
Characterization of human A(2B) **adenosine** receptors: radioligand binding, western blotting, and coupling to G(q) in human embryonic kidney 293 cells and HMC-1 mast cells.
Linden J; Thai T; Figler H; Jin X; Robeva AS
Department of Internal Medicine, University of Virginia, Charlottesville, Virginia, USA. jlinden@virginia.edu
Molecular pharmacology (UNITED STATES) Oct 1999, 56 (4) p705-13, ISSN 0026-895X Journal Code: NGR
Contract/Grant No.: RO1-HK37942, PHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Recombinant human A(2B) **adenosine** receptors (A(2B)ARs) and receptors extended on the amino terminus with hexahistidine and the FLAG -epitope, DYKDDDDK (H/F-A(2B)) were stably overexpressed (to >20,000 fmol/mg protein) in human embryonic kidney 293 cells (HEK-A(2B)). By Western blotting, the H/F-A(2B) receptor runs as a 34.8-kDa glycoprotein. Pharmacological properties of A(2B)ARs were characterized with

(125)I-3-aminobenzyl-8-phenyl-(4-oxyacetic acid)-1-propylxanthine (K(D), 36 nM). In competition binding assays, the affinity of agonists is reduced by substitution on either the N(6)- or the C-2 position of the adenine ring, whereas 5'-substitutions increase affinity, resulting in the potency order: 5'-N-ethylcarboxamidoadenosine (NECA) >> N(6)-aminobenzyl-NECA approximately 2-chloroadenosine > 2-[4-(2-carboxyethyl)phenethylamino]-NECA (CGS21680) > N(6)-aminobenzyladenosine. The A(2B)AR is potently blocked by the A(2A)-selective **antagonist** 4-(2-[7-amino-2-[2-furyl][1,2,4]triazolo-[2,3-a][1,3,5] triazin-5-yl-amino]ethyl)phenol (ZM241385; K(I), 32 nM for A(2B), 1.4 nM for A(2A)) and the A(1) selective **antagonist** 8-cyclopentyl-1,3-dipropylxanthine (K(I), 50.5 nM for A(2B); 2.5 nM for A(1)). The K(I) values for the antiasthmatic xanthines, theophylline (7.8 microM) and enprofylline (6.4 microM), are below their therapeutic plasma concentrations (20 to 50 microM), and agree with K(I) determinations for inhibition of NECA-stimulated cAMP accumulation in HEK-A(2B) cells. NECA or N(6)-(3-iodo)benzyl-5'-N-methylcarboxamidodoadenosine (IB-MECA) stimulate inositol trisphosphates and calcium accumulation in HEK-A(2B) or HEK-A(3) cells, respectively, but only the A(3) response is prevented by pertussis toxin. In human HMC-1 mast cells, A(2B)AR activation stimulates calcium mobilization and cAMP accumulation. We conclude that HEK-A(2B) cells and HMC-1 mast cells possess A(2B)AR glycoproteins that are coupled to both G(q/11 and G(s).

2/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10334444 99129927 PMID: 9933147
Signaling via A2A **adenosine** receptor in four PC12 cell clones.
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Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Jan 1999, 359 (1) p28-32, ISSN 0028-1298 Journal Code: NTQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
PC12 cells are genetically labile and so-called wild-type cells comprise multiple subclones. We have examined the A2A **adenosine** receptor signal transduction pathways in four such clones (denoted clones 1, 19, 21 and 27) of PC12 cells. **Adenosine** A2A, **A2B** and A1 receptor mRNAs were detected in all four clones by RT-PCR, whereas no A3 receptor mRNA was found. A2A receptors were quantitated by radioligand binding using the **antagonist** radioligand [3H]SCH 58261 ([3H]-5-amino-7(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4 triazolo [1,5-c] pyrimidine). The Bmax was highest in clone 1 followed by clones 21, 19 and 27. Whereas the amount of G(i) protein appeared similar in all four clones, the amount of G(s) protein was higher in clones 21 and 27 than in the other two clones. Maximal responses to the non-selective **adenosine** analogue NECA (5'-N-ethylcarboxamidoadenosine) were similar to those observed with the selective **adenosine** A2A receptor agonist CGS 21680 (2-[p-(2-carbonylethyl) phenylethylamino]-5'-N-ethylcarboxamidoadenosine), and were approximately equal in clones I and 21, but lower in clone 19 and very low in clone 27. For both compounds EC50 was significantly higher in clone 27 than in clone 1. In both clones the response to NECA could be competitively antagonized by a selective **adenosine** A2A **antagonist**, SCH 58261. The present results show that different clones of PC 12 cells differ widely in the cAMP increase induced by **adenosine** analogues and that this is due to differences in the amount of **adenosine** A2A receptor, G protein and effector. A large difference in receptor number resulted in differences in potency of an agonist.

2/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10193487 99300037 PM[redacted] 10372822

Adenosine mediates relaxation of human small resistance-like coronary arteries via **A2B** receptors.

Kemp BK; Cocks TM

Department of Pharmacology, The University of Melbourne, Parkville, Victoria, Australia.

British journal of pharmacology (ENGLAND) Apr 1999, 126 (8) p1796-800, ISSN 0007-1188 Journal Code: B00

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

1. The receptor subtype and mechanisms underlying relaxation to **adenosine** were examined in human isolated small coronary arteries contracted with the thromboxane A2 mimetic, 1,5,5-hydroxy-11alpha, 9alpha (epoxymethano)prosta-5Z, 13E-dienoic acid (U46619) to approximately 50% of their maximum contraction to K+ (125 mM) depolarization (Fmax). Relaxations were normalized as percentages of the 50% Fmax contraction. 2. **Adenosine** caused concentration-dependent relaxations (pEC50, 5.95+/-0.20; maximum relaxation (Rmax), 96.7+/-1.4%) that were unaffected by either combined treatment with the nitric oxide inhibitors, NG-nitro-L-arginine (L-NOARG; 100 microM) and oxyhaemoglobin (HbO; 20 microM) or the ATP-dependent K+ channel (KATP) inhibitor, glibenclamide (10 microM). The pEC50 but not Rmax to **adenosine** was significantly reduced by high extracellular K+ (30 mM). Relaxations to the adenylate cyclase activator, forskolin, however, were unaffected by high K+ (30 mM). 3. **Adenosine** and a range of **adenosine** analogues, **adenosine**, 2-chloroadenosine (2-CADO), 5'-N-ethyl-carboxamidoadenosine (NECA), R(-)-N6-(2-phenylisopropyl)-**adenosine** (R-PIA), S(+)-N6-(2-phenylisopropyl)-**adenosine** (S-PIA), N6-cyclopentyladenosine (CPA), 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl-beta- D-ribofuranuronamide (IB-MECA), 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamido **adenosine** hydrochloride (CGS 21680), relaxed arteries with a rank order of potency of NECA= 2-CADO >**adenosine**= IB-MECA = R-PIA= CPA > S-PIA)> CGS 21680. 4. Sensitivity but not Rmax to **adenosine** was significantly reduced approximately 80 and 20 fold by the A1-selective **adenosine** receptor **antagonist**, 8-(p-sulphophenyl)theophylline (8-SPT) and the A2 receptor **antagonist**, 3,7-dimethyl-1-propargylxanthine (DMPX). By contrast, the A1-selective **antagonist**, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) had no effect on pEC50 or Rmax to **adenosine**. 5. These results suggest that **A2B** receptors mediate relaxation to **adenosine** in human small coronary arteries which is independent of NO but dependent in part on a K+-sensitive mechanism.

2/3,AB/27 (Item 27 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10068106 99137564 PMID: 9950763

Adenosine and its nucleotides activate wild-type and R117H CFTR through an **A2B** receptor-coupled pathway.

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Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama 35294-0005, USA.

American journal of physiology (UNITED STATES) Feb 1999, 276 (2 Pt 1) pC361-9, ISSN 0002-9513 Journal Code: 3U8

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Languages: ENGLISH

Document type: Journal Article

Record type: Completed

ATP and its metabolites stimulate Cl- secretion in human epithelium in vitro and in vivo. The specific purinergic receptor subtypes that govern these effects have been difficult to separate, in part due to multiple parallel pathways for Cl- secretion in respiratory and intestinal

epithelia. In a simplified model using COS-7 cells, we demonstrate acquisition of an ATP, ADP-, AMP-, and **adenosine** (A[redacted] regulated halide permeability specifically following expression of wild-type (wt) cystic fibrosis transmembrane conductance regulator (CFTR). This halide permeability is blocked by the P1 purinergic receptor **antagonist** 8-phenyl theophylline, sensitive to the protein kinase A inhibitor H-89, and associated with a modest, dose-dependent increase in cellular cAMP concentration. Phorbol esters poorly activate halide permeability compared with ADO, and ADO-stimulated efflux was not affected by treatment with the protein kinase C inhibitor bisindolylmaleimide I. The A2 ADO receptor (AR) agonists 5'-N-ethylcarboxamide **adenosine** and ADO were strong activators, whereas the A1 AR agonist R-phenylisopropyladenosine failed to activate halide permeability. Metabolic conversion of ADO nucleotides by surface ecto-5'-nucleotidase to more active (less phosphorylated) forms contributes to anion transport activation in these cells. Immunoprecipitation with anti-**A2B** AR antibody identified a 31-kDa protein in both COS-7 and human bronchial epithelial cells. Together, these findings indicate that ADO and its nucleotides are capable of activating wtCFTR-dependent halide permeability through **A2B** AR and that this AR subtype is present in human bronchial epithelium. We also present data showing that this pathway can activate clinically significant mutant CFTR molecules such as R117H.

2/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10059327 99115795 PMID: 9914278
Intraneuronal [Ca2+] changes induced by 2-deoxy-D-glucose in rat hippocampal slices.
Tekkok S; Medina I; Krnjevic K
Department of Anaesthesia Research and Department of Physiology, McGill University, Montreal, Quebec H3G 1Y6, Canada.
Journal of neurophysiology (UNITED STATES) Jan 1999, 81 (1) p174-83, ISSN 0022-3077 Journal Code: JC7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Temporary replacement of glucose by 2-deoxyglucose (2-DG; but not sucrose) is followed by long-term potentiation of CA1 synaptic transmission (2-DG LTP), which is Ca2+-dependent and is prevented by dantrolene or N-methyl-D-aspartate (NMDA) antagonists. To clarify the mechanism of action of 2-DG, we monitored [Ca2+]i while replacing glucose with 2-DG or sucrose. In slices (from Wistar rats) kept submerged at 30 degreesC, pyramidal neurons were loaded with [Ca2+]-sensitive fluo-3 or Fura Red. The fluorescence was measured with a confocal microscope. Bath applications of 10 mM 2-DG (replacing glucose for 15 +/- 0.38 min, means +/- SE) led to a rapid but reversible rise in fluo-3 fluorescence (or drop of Fura Red fluorescence); the peak increase of fluo-3 fluorescence (DeltaF/F0), measured near the end of 2-DG applications, was by 245 +/- 50% (n = 32). Isosmolar sucrose (for 15-40 min) had a smaller but significant effect (DeltaF/F0 = 94 +/- 14%, n = 10). The 2-DG-induced DeltaF/F0 was greatly reduced (to 35 +/- 15%, n = 16) by,-aminophosphono-valerate (50-100 microM) and abolished by 10 microM dantrolene (-4.0 +/- 2.9%, n = 11). A substantial, although smaller effect, of 2-DG persisted in Ca2+-free 1 mM ethylene glycol-bis(beta-aminoethyl ether)-N,N,N', N'-tetraacetic acid (EGTA) medium. Two **adenosine** antagonists, which do not prevent 2-DG LTP, were also tested; 2-DG-induced DeltaF/F0 (fluo-3) was not affected by the A1 **antagonist** 8-cyclopentyl-3, 7-dihydro-1,3-dipropyl-1H-purine-2 ,6-dione (DPCPX 50 nM; 287 +/- 38%; n = 20), but it was abolished by the A1/A2 **antagonist** 8-SPT; 25 +/- 29%, n = 19). These observations suggest that 2-DG releases glutamate and **adenosine** and that the rise in [Ca2+] may be triggered by a synergistic action of glutamate (acting via NMDA receptors) and **adenosine** (acting via **A2b** receptors) resulting in Ca2+ release from a dantrolene-sensitive store. The discrepant

effects of sucrose and 8-SPT on DeltaF/F0, on the one hand, and 2-DG LTP, on the other, support other evidence that increases in postsynaptic [Ca2+]i are not essential for 2-DG LTP.

2/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10056313 99079371 PMID: 9863667
Characterization of **adenosine** receptors evoking excitation of mesenteric afferents in the rat.
Kirkup AJ; Eastwood C; Grundy D; Chessell IP; Humphrey PP
Department of Biomedical Science, University of Sheffield, Western Bank.
British journal of pharmacology (ENGLAND) Nov 1998, 125 (6) p1352-60, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We examined the effects of **adenosine** receptor agonists and antagonists on the discharge of mesenteric afferent nerves supplying the jejunum in pentobarbitone sodium-anaesthetized rats. **Adenosine** (0.03-10 mg kg(-1), i.v.), NECA (0.3-300 microg kg(-1), i.v.) and the A1 receptor agonist, GR79236 (0.3-1000 microg kg(-1), i.v.), each induced dose-dependent increases in afferent nerve activity and intrajejunal pressure, hypotension and bradycardia. The A1 receptor **antagonist**, DPCPX (3 mg kg(-1), i.v.), antagonized all the effects of GR79236 but only the haemodynamic effects of **adenosine** and NECA. The A2A receptor **antagonist**, ZM241385 (3 mg kg(-1), i.v.), antagonized the hypotensive effect of NECA but none of the effects of GR79236. The A2A receptor agonist, CGS21680 (0.3-300 microg kg(-1), i.v.), and the A3 receptor agonist, IB-MECA (0.3-300 microg kg(-1), i.v.), each induced only a dose-dependent hypotension. Subsequent administration of **adenosine** (3 mg kg(-1), i.v.) induced increases in afferent nerve activity and intrajejunal pressure and bradycardia. ZM241385 (3 mg kg(-1), i.v.) antagonized the hypotensive effect of CGS21680 but not the effects of **adenosine** . Bethanechol (300 microg kg(-1), i.v.) evoked increases in afferent nerve activity and intrajejunal pressure, hypotension and bradycardia. However, **adenosine** (3 mg kg(-1), i.v.) evoked greater increases in afferent nerve activity than bethanechol despite inducing smaller increases in intrajejunal pressure. In summary, A1 and **A2B** and/or **A2B**-like receptors evoke **adenosine**-induced increases in mesenteric afferent nerve activity and intrajejunal pressure in the anaesthetized rat. Furthermore, elevations in intrajejunal pressure do not wholly account for **adenosine**-evoked excitation of mesenteric afferent nerves.

2/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10035025 99130080 PMID: 9931103
Adenosine inhibits collagen and total protein synthesis in vascular smooth muscle cells.
Dubey RK; Gillespie DG; Jackson EK
Center for Clinical Pharmacology, University of Pittsburgh Medical Center, PA 15213-2582, USA. dubey@novell2.dept-med.pitt.edu
Hypertension (UNITED STATES) Jan 1999, 33 (1 Pt 2) p190-4, ISSN 0194-911X Journal Code: GK7
Contract/Grant No.: HL 35909, HL, NHLBI; HL 55314, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The objective of this study was to characterize the effects of exogenous, drug-induced and cAMP-**adenosine** pathway-derived **adenosine** on collagen synthesis by and hypertrophy of vascular smooth muscle cells

(SMCs). Confluent vascular SMCs were stimulated with 2.5% fetal calf serum in the presence and absence of **adenosine** receptor agonists [**adenosine**, 2-chloroadenosine, N6-cyclopentyladenosine, 5'-N-ethylcarboxamidoadenosine, 5'-N-methylcarboxamidoadenosine, and 2-p-(2-carboxyethyl) phenethylamino-5'-N-ethylcarboxamino **adenosine**], drugs that increase levels of endogenous **adenosine** [erythro-9-(2-hydroxy-3-nonyl) adenine, dipyridamole, and iodotubericidin], and cAMP (increases **adenosine** by conversion to AMP and hence to **adenosine** via the cAMP-**adenosine** pathway). **Adenosine** receptor agonists inhibited fetal calf serum-induced collagen and total protein synthesis (as assessed by [3H]proline and [3H]leucine incorporation, respectively) with a relative potency profile consistent with the effects being mediated by **adenosine A2B** receptors. Erythro-9-(2-hydroxy-3-nonyl) adenine, dipyridamole, iodotubericidin, and cAMP also inhibited collagen and total protein synthesis. The effects of 2-chloroadenosine, erythro-9-(2-hydroxy-3-nonyl) adenine, iodotubericidin, and cAMP on collagen and total protein synthesis were attenuated by KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine (selective and nonselective A2 receptor antagonists, respectively) but not by 8-cyclopentyl-1,3-dipropylxanthine (selective A1 receptor **antagonist**). These studies indicate that exogenous, drug-induced and cAMP-**adenosine** pathway-derived **adenosine** inhibit vascular SMC collagen synthesis and hypertrophy via **A2B** receptors. Thus, exogenous **A2B** receptor agonists and drugs that modulate endogenous **adenosine** levels may protect against vasoocclusive disorders by attenuating extracellular matrix synthesis by and cellular hypertrophy of vascular SMCs. Moreover, the cAMP-**adenosine** pathway may protect against vascular hypertrophy.

2/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10016059 99117014 PMID: 9920286
Differences in the order of potency for agonists but not antagonists at human and rat **adenosine** A2A receptors.
Kull B; Arslan G; Nilsson C; Owman C; Lorenzen A; Schwabe U; Fredholm BB
Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Biochemical pharmacology (ENGLAND) Jan 1 1999, 57 (1) p65-75, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To examine possible species differences in pharmacology, rat **adenosine** A2A receptors were studied in PC12 (pheochromocytoma) cells, and human receptors in Chinese hamster ovary (CHO) cells transfected with the cloned human A2A receptor cDNA. Using [3H]-5-amino-7(2-phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo [1,5-c]pyrimidine ([3H]-SCH 58261) as radioligand, the estimated Bmax (maximal binding) was 538 and 2085 fmol/mg in CHO and PC12 cells, respectively. The Kd (dissociation constant) values for [3H]-SCH 58261 were 1.05 and 5.6 nM in the two cell types, respectively. The order of potency of antagonists and most agonists was the same in both cell types, but 2-phenylaminoadenosine and 2-chloroadenosine were relatively less potent in PC12 cells than in CHO cells. In the functional assay, using cyclic AMP accumulation, all agonists tested were more potent in CHO than in PC12 cells, but this could not be readily explained by differences in adenylyl cyclase or in the expression of G proteins. As in the case of binding, the relative agonist potencies were similar for most compounds, but 2-phenylaminoadenosine and 2-chloroadenosine were more potent at human A2A receptors in CHO cells than predicted from the data obtained on rat A2A receptors in PC12 cells. Antagonists were approximately equipotent in the two cells. These results show that, despite only small differences in amino acid sequences and no difference in **antagonist** pharmacology, the relative order of potency of receptor agonists can differ between species

homologues of the **adenosine** A2A receptor.

2/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09928906 98387476 PMID: 9722021
Adenosine regulates tissue factor expression on endothelial cells.
Deguchi H; Takeya H; Urano H; Gabazza EC; Zhou H; Suzuki K
Department of Molecular Pathobiology, Mie University School of Medicine, Tsu-city, Japan.
Thrombosis research (UNITED STATES) Jul 15 1998, 91 (2) p57-64, ISSN 0049-3848 Journal Code: VRN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The aim of this study was to evaluate the inhibitory activity of **adenosine** on tumor necrosis factor-alpha (TNF), thrombin-, or phorbol 12-myristate 13-acetate (PMA)-induced tissue factor (TF) expression on human umbilical vein endothelial cells (HUVECs). This inhibitory effect of **adenosine** was found to be counteracted by the non-selective **adenosine** receptor (AR) **antagonist**, 8-(p-sulfophenyl) theophylline. To clarify the role of ARs (A1, A2a, **A2b**, and A3) in this regulation, we evaluated the effect of several agonists and antagonists specific for AR-subclass on TF expression. The selective A2aAR agonist, 2-p-(2-carboxyethyl) phenethylamino-5'-N-ethylcarboxamido **adenosine** hydrochloride (CGS 21680), the A3AR agonist, N6-2-(4-aminophenyl) ethyladenosine (APNEA), and the A1AR **antagonist**, 1,3-dipropyl-8-(2-amino-4-chlorophenyl) xanthine (PACPX) each inhibited TF activity expression induced by TNF, thrombin, or PMA on HUVECs. In contrast, the selective A1AR agonist, chloro-N6-cyclopentyladenosine (CCPA) and the A2AR **antagonist**, 3,7-dimethyl-1-propargylxanthine (DMPX) enhanced each stimulant-induced TF activity expression. All agonist or **antagonist** alone did not alter the basal TF expression on HUVECs. Our results suggest that stimulation of A2aAR and A3AR down-regulates and that of A1AR up-regulates the endothelial cell TF expression induced by TNF, PMA, or thrombin. Thus, it appears that **adenosine** itself may exert anticoagulant activity on vascular endothelial cells via its A2a and A3 receptors, particularly during ischemic or atherosclerotic processes which are known to be associated with local increased levels of **adenosine**.

2/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09884346 98346556 PMID: 9683026
NF279: a novel potent and selective **antagonist** of P2X receptor-mediated responses.
Damer S; Niebel B; Czeche S; Nickel P; Ardanuy U; Schmalzing G; Rettinger J; Mutschler E; Lambrecht G
Department of Pharmacology, Biocentre Niederursel, University of Frankfurt, Frankfurt/M., Germany.
European journal of pharmacology (NETHERLANDS) May 29 1998, 350 (1) pR5-6, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
8,8'-(Carbonylbis(imino-4, 1 -phenylenecarbonylimino-4,1-phenylenecarbonylimino))bis(1,3, 5-naphthalenetrisulfonic acid) (NF279) antagonized P2X receptor-mediated contractions in rat vas deferens, evoked by alpha,beta-methylene ATP (10 microM; pIC50=5.71) without affecting responses mediated via alpha1A-adrenoceptors, **adenosine** A1 and **A2B** receptors, histamine H1, muscarinic M3 and nicotinic receptors. The low inhibitory potency of NF279 on P2Y receptors in guinea-pig taenia coli (pA2=4.10) and at ecto-nucleotidases in folliculated Xenopus laevis

oocytes (IC50 > 100 microM) indicates that NF279 is a novel specific and selective P2X receptor **antagonist**.

2/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09884053 98338222 PMID: 9673434
Evidence for the presence of both P1 and P2 purinoceptors in the rat myometrium.
Gillman TA; Pennefather JN
Department of Pharmacology, Monash University, Clayton, Victoria, Australia.
Clinical and experimental pharmacology & physiology (AUSTRALIA) Jul-Aug 1998, 25 (7-8) p592-9, ISSN 0305-1870 Journal Code: DD8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. **Adenosine**, **adenosine** triphosphate (ATP) and some stable analogues of **adenosine** inhibited field stimulation-induced contractions of the uterus from rats treated with oestradiol cypionate (20 micrograms/kg, s.c.) 1 day previously. **Adenosine** was twice as potent as ATP; both were potentiated by dipyridamole (10 mumol/L). 2. The order of agonist potency of **adenosine** and its analogues was: 5'-N-ethylcarboxamidoadenosine (NECA) > N6-cyclohexyladenosine > or = R-phenylisopropyladenosine = S-phenylisopropyladenosine = 2-chloroadenosine > or = **adenosine** > or = ATP > > 2-p-(2-carboxyethyl) phenethylamino-5'-N-ethylcarboxamidoadenosine. This order suggests the presence of P1 purinoceptors of the **A2B** subtype. 3. Responses to agonists were antagonized to differing extents by the P1 purinoceptor **antagonist** 8-phenyltheophylline (10 mumol/L). 4. In uterine preparations from rats pretreated for 2 days with oestrogen (20 micrograms/kg, s.c.) and for 1 day with progesterone (3 mg/animal, s.c.), the inhibitory potencies of **adenosine** and NECA were reduced, indicating hormonal regulation of uterine responsiveness to P1 purinoceptor agonists. 5. Stable analogues of ATP caused contractions of unstimulated myometrial preparations from oestrogen-treated animals, indicating activation of a P2 purinoceptor, possibly of the P2X subtype, because of the relative order of potency was alpha, beta-methylene ATP > beta, gamma-methylene ATP = ATP = 2-methylthio ATP.

2/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09859818 98312447 PMID: 9648628
A2 **adenosine** receptors in Mongolian gerbil middle ear epithelium and their regulation of Cl- secretion.
Furukawa M; Ikeda K; Oshima T; Suzuki H; Yamaya M; Sasaki H; Takasaka T
Department of Otorhinolaryngology, Tohoku University School of Medicine, Sendai, Japan.
Acta physiologica Scandinavica (ENGLAND) May 1998, 163 (1) p103-12, ISSN 0001-6772 Journal Code: 1U4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The present study investigates the effects of **adenosine** and its analogues on Cl- secretion in primary cultures of gerbil middle ear epithelium. Short-circuit current (Isc), an index of transepithelial active transport, was measured on the same cells cultured on porous filters. Baseline Isc and transepithelial resistance were 27.0 +/- 0.7 microA cm-2 and 275 +/- 7 omega cm2, respectively (n = 178). Extracellular **adenosine** and its analogues elicited a sustained increase in Isc when added to apical or basolateral surfaces. Both the A2A selective agonist 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamido **adenosine**

and the A2A/**A2B** non-selective agonist 5'-(N-ethyl-carboxamido) **adenosine** (NECA) increased Isc, but NECA was more effective than CGS21680. A1 selective **antagonist** 8-cyclopentyl-1,3-dipropylxanthine did not reduce NECA-induced Isc. These results suggest the presence of both A2A and **A2B** receptors. NECA did not stimulate a rise in the intracellular Ca2+ concentration ([Ca2+]i) in single middle ear epithelial cells cultured on glass coverslips. Dibutyryl cAMP (dbcAMP) induced an initial transient increase in Isc followed by the sustained plateau. Addition of dbcAMP also caused a transient increase in [Ca2+]i. The protein kinase A inhibitor, N-[2-(p-bromocinnamylamino)ethyl]-5-isoquinolinesulfonamide, greatly reduced the increase in the Isc responses to NECA. 1,2-Bis-(2-aminophenoxy)ethane N,N,N',N'-tetraacetic acid-acetoxymethyl ester influenced neither the NECA-induced increase in Isc nor the dbcAMP-induced sustained phase of Isc, but greatly inhibited the dbcAMP-induced transient increase in Isc. Glibenclamide, a cystic fibrosis transmembrane conductance regulator (CFTR) channel inhibitor, reduced the NECA-induced Isc. These results indicate that extracellular **adenosine** and its analogues activate the cAMP-protein kinase A system, but not intracellular Ca(2+)-dependent mechanisms, leading to Cl- secretion, possibly through the CFTR Cl- channels in the cultured gerbil middle ear epithelium.

2/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09846903 98332625 PMID: 9666151
Adenosine receptor mediated stimulation of intracellular calcium in acutely isolated astrocytes.
Pilitsis JG; Kimelberg HK
Division of Neurosurgery, A-60, Department of Pharmacology and Neuroscience, Albany Medical College, 47 New Scotland Avenue, Albany, NY 12208, USA.
Brain research (NETHERLANDS) Jul 6 1998, 798 (1-2) p294-303, ISSN 0006-8993 Journal Code: B5L
Contract/Grant No.: NS 19492, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The characteristics of **adenosine** receptors found in glial fibrillary acid protein (GFAP)-positive astrocytes acutely isolated from the cerebral cortices of 4- to 12-day old rats were examined by evaluating the effects of **adenosine** and its analogues on intracellular calcium levels. First, these effects were compared with those seen in primary astrocytic cultures, and it was found that acutely isolated astrocytes showed much greater sensitivity to **adenosine** than their cultured counterparts. Then, the **adenosine** evoked calcium responses in acutely isolated cells were evaluated under various conditions. The responses to **adenosine** were not inhibited by papaverine, an uptake blocker, or by removal of extracellular calcium. U73122, a phospholipase C inhibitor, was able to completely inhibit the **adenosine** response. The receptor inhibitor 8-isobutyl-1-methylxanthine inhibited the calcium response to **adenosine**, providing evidence that the response is not coupled to the xanthine-insensitive A3 receptor. The stimulatory action of NECA, a non-selective analogue, was blocked neither by the A2A-selective receptor **antagonist** 8-(3-chlorostyryl) caffeine nor by the A1-selective receptor **antagonist** 8-cyclopentyl-1,3-dipropylxanthine. The **A2B** receptor **antagonist** alloxazine, however, was able to completely inhibit the increase in intracellular calcium produced by NECA. Taken together, these data suggest that the **adenosine** -evoked calcium response in acutely isolated astrocytes is coupled to the **A2B** receptor. Copyright 1998 Elsevier Science B.V. All rights reserved.

2/3,AB/37 (Item 37 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09813[illegible] 98334695 PMID: 9667972

Derivatives of the triazoloquinazoline **adenosine antagonist** (CGS 15943) having high potency at the human **A2B** and A3 receptor subtypes.

Kim YC; de Zwart M; Chang L; Moro S; von Frijtag Drabbe Kunzel JK; Melman N; IJzerman AP; Jacobson KA

Molecular Recognition Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892-0810, USA.

Journal of medicinal chemistry (UNITED STATES) Jul 16 1998, 41 (15) p2835-45, ISSN 0022-2623 Journal Code: J0F

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The **adenosine antagonist** 9-chloro-2-(2-furanyl)[1,2,4]triazolo[1,5-c]quinazolin-5-amine (CGS 15943) binds nonselectively to human A1, A2A, and A3 receptors with high affinity. Acylated derivatives and one alkyl derivative of the 5-amino group and other modifications were prepared in an effort to enhance **A2B** or A3 subtype potency. In general, distal modifications of the N5-substituent were highly modulatory to potency and selectivity at **adenosine** receptors, as determined in radioligand binding assays at rat brain A1 and A2A receptors and at recombinant human A3 receptors. In Chinese hamster ovary cells stably transfected with human **A2B** receptor cDNA, inhibition of agonist-induced cyclic AMP production was measured. An N5-(2-iodophenyl)acetyl derivative was highly selective for A2A receptors. An (R)-N5-alpha-methyl(phenylacetyl) derivative was the most potent derivative at A3 receptors, with a Ki value of 0.36 nM. A bulky N5-diphenylacetyl derivative, 13, displayed a Ki value of 0.59 nM at human A3 receptors and was moderately selective for that subtype. Thus, a large, nondiscriminating hydrophobic region occurs in the A3 receptor in proximity to the N5-substituent. A series of straight-chain N5-aminoalkylacyl derivatives demonstrated that for **A2B** receptors the optimal chain length occurs with three methylene groups, i.e., the N5-gamma-aminobutyryl derivative 27 which had a pA2 value of 8.0 but was not selective for **A2B** receptors. At A1, A2A, and A3 receptors however the optimum occurs with four methylene groups. An N5-pivaloyl derivative, which was less potent than 27 at A1, A2A, and A3 receptors, retained moderate potency at **A2B** receptors. A molecular model of the 27-**A2B** receptor complex based on the structure of rhodopsin utilizing a "cross-docking" procedure was developed in order to visualize the environment of the ligand binding site.

2/3,AB/38 (Item 38 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09699855 98195096 PMID: 9535419

Adenosine inhibits collagen and protein synthesis in cardiac fibroblasts: role of **A2B** receptors.

Dubey RK; Gillespie DG; Jackson EK

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Hypertension (UNITED STATES) Apr 1998, 31 (4) p943-8, ISSN 0194-911X Journal Code: GK7

Contract/Grant No.: HL 35909, HL, NHLBI; HL 55314, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The objective of this study was to characterize the effects of exogenous and endogenous (cardiac fibroblast-derived) **adenosine** on [3H]proline and [3H]leucine incorporation, which are reliable markers of collagen and total protein synthesis, respectively, in rat left ventricular cardiac

fibroblasts. Growth-arrested confluent cardiac fibroblast monolayers were stimulated with 2.5% fetal calf serum (FCS) in the presence and absence of **adenosine**, 2-chloroadenosine (stable **adenosine** analogue), or modulators of **adenosine** levels including (1) erythro-9-(2-hydroxy-3-nonyl) adenine (**adenosine** deaminase inhibitor), (2) dipyridamole (**adenosine** transport blocker), and (3) iodotubericidin (**adenosine** kinase inhibitor). All agents inhibited in a concentration-dependent fashion FCS-induced [3H]proline and [3H]leucine incorporation. These effects were blocked by KF17837 (selective A2 **antagonist**) and 1,3-dipropyl-8-(p-sulfophenyl)xanthine (A1/A2 receptor **antagonist**) but not by 8-cyclopentyl-1,3-dipropylxanthine (selective A1 **antagonist**), thus excluding the participation of A1 receptors. The lack of effect of CGS21680 (selective A2A agonist) excluded involvement of A2A receptors, thus suggesting a major role for **A2B** receptors. Comparisons of the inhibitory potencies of N6-cyclopentyladenosine (selective A1 agonist), 5'-N-ethylcarboxamidoadenosine (A1/A2 agonist), and 5'-N-methylcarboxamidoadenosine (A1/A2 agonist) were consistent with that of an **A2B** receptor subtype mediating the inhibitory effects. We conclude that **adenosine** inhibits FCS-induced collagen and total protein synthesis in cardiac fibroblasts via activation of **A2B** receptors. These studies suggest, but do not prove, that endogenous **adenosine** may protect against cardiac fibrosis.

2/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09696819 98175324 PMID: 9515573
Pharmacological characterization of **adenosine A2B** receptors: studies in human mast cells co-expressing A2A and **A2B adenosine** receptor subtypes.
Feoktistov I; Biaggioni I
Department of Medicine, Vanderbilt University, Nashville, TN 37232-2195, USA.
Biochemical pharmacology (ENGLAND) Mar 1 1998, 55 (5) p627-33, ISSN 0006-2952 Journal Code: 9Z4
Contract/Grant No.: R29HL55596, HL, NHLBI; RR00095, RR, NCRR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Characterization of **A2B** receptors is hampered by the lack of selective pharmacological probes and often relies on their relative affinity to agonists that are selective at other receptor types. This approach is limited because the affinity of **A2B** receptors for putative A3 agonists has not been determined. Using the human erythroleukemia cell line HEL as a cellular model for **A2B**-mediated adenylate cyclase activation, we found the following potencies (pD2) for the non-selective agonist 5'-N-ethylcarboxamidoadenosine (NECA) (5.65 +/- 0.04), the putative A3 agonists N6-benzyl-NECA (4.17 +/- 0.06) and N6-(3-iodobenzyl)-N-methyl-5'-carbamoyladenosine (IB-MECA) (3.7 +/- 0.02), and the A2A agonist 4-[(N-ethyl-5'-carbamoyladenos-2-yl)-aminoethyl]-phenyl propionic acid (CGS21680) (2.8 +/- 0.1). Because of the lack of a selective agonist, characterization of **A2B** receptor function is difficult in cells co-expressing A2A receptors. In the human mast cell line HMC-1, NECA induced cAMP accumulation with a concentration-response relationship best fitted to a two-sited model (pD2 7.69 +/- 0.42 and 5.92 +/- 0.21 for high- and low-affinity sites), suggesting the presence of both A2A and **A2B** receptors in these cells. We demonstrated that **A2B** receptors can be selectively activated with NECA in the presence of the selective A2A **antagonist** 5-amino-7-(phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (SCH 58261). Under these conditions, the concentration-response relationship of NECA for cyclic AMP accumulation was now best fitted to a one-site model (pD2 5.68 +/- 0.03, Hill slope 0.93 +/- 0.06, 95 confidence intervals 0.8 to 1.06) corresponding to selective activation of **A2B** receptors. Using the approaches developed in this

study, we determined that **A2B**, and not A2A or A3, receptors account for all the calcium mobilization induced by NECA in HMC-1 cells.

2/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09696867 98175321 PMID: 9515570
Evidence for co-expression and desensitization of A2a and **A2b** **adenosine** receptors in NG108-15 cells.
Mundell SJ; Kelly E
Department of Pharmacology, School of Medical Sciences, University of Bristol, UK.
Biochemical pharmacology (ENGLAND) Mar 1 1998, 55 (5) p595-603, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Using receptor-selective agonists and antagonists, the possible presence of both A2a and **A2b** **adenosine** receptor subtypes coupled to activation of adenylyl cyclase was investigated in NG108-15 neuroblastoma x glioma hybrid cells. The relatively non-selective **adenosine** receptor agonist 5'-(N-ethyl carboxamido)-**adenosine** (NECA; 1 nM-300 microM) produced a biphasic increase in adenylyl cyclase activity in cell homogenates, best fitted to two components with high (EC50 0.7 microM) and low (EC50 16.0 microM) potency, respectively. The selective **adenosine** A2a receptor agonist CGS-21680 (1 nM-300 microM) also produced a biphasic increase in adenylyl cyclase. The NECA-dependent increase in adenylyl cyclase activity was almost completely inhibited by the non-selective **adenosine** receptor **antagonist** xanthine amine congener (XAC; 30 microM), but only partially inhibited by the selective A2a **adenosine** **antagonist** 8-(3-chlorostyryl)caffeine (CSC; 1 microM). Experiments were also performed to investigate the time course of NECA-induced desensitization of putative A2a and **A2b** receptor responses. The A2a-response was quantified using 10 microM CGS-21680, whilst the **A2b** response was quantified using 100 microM NECA in the presence of 1 microM CSC. The t0.5 for desensitization for each subtype was found to be around 20 min. Neither activation (with dibutyryl cAMP; 1 mM) nor inhibition (with H-89; 10 microM) of cyclic AMP-dependent protein kinase altered the ability of NECA pretreatment to desensitize A2a or **A2b** receptor-activated adenylyl cyclase. However zinc (200 microM), an inhibitor of G-protein coupled receptor kinase 2 (GRK2), significantly reversed the agonist-induced desensitization of A2a and **A2b** receptor-activated adenylyl cyclase. These experiments suggest the co-existence of A2a and **A2b** receptors coupled in a stimulatory fashion to adenylyl cyclase in NG108-15 cells. Furthermore desensitization of A2a and **A2b** responses occurs at the same rate and may involve a G-protein-coupled receptor kinase.

2/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09694145 98173749 PMID: 9495868
The A2A **adenosine** receptor mediates coronary vasodilation.
Belardinelli L; Shryock JC; Snowdy S; Zhang Y; Monopoli A; Lozza G; Ongini E; Olsson RA; Dennis DM
Department of Medicine, College of Medicine, University of Florida, Gainesville, USA. ramsepd@medicine.ufl.edu
Journal of pharmacology and experimental therapeutics (UNITED STATES) Mar 1998, 284 (3) p1066-73, ISSN 0022-3565 Journal Code: JP3
Contract/Grant No.: N01-HL-56785, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The coronary vasodilation caused by **adenosine** is due to activation of A2 **adenosine** receptors (A2AdoRs), but the subtype or subtypes of A2AdoR (A2A and/or **A2B**) that mediate this action are uncertain. The purpose of this study was to test the hypothesis that A2AAdoRs mediate coronary vasodilation caused by exogenous or endogenous **adenosine** in the guinea pig isolated perfused heart. The newly described A2AAdoR **antagonist** SCH58261 was used to selectively block A2AAdoRs. Attenuations by SCH58261 of increases in coronary conductance (A2 response) and of atrioventricular nodal conduction time (A1 response) caused by exogenous and endogenous **adenosine** and by agonists with relative selectivity for A2A and A1AdoRs were measured. The CGS21680-induced increase of coronary conductance was antagonized by SCH58261 in a concentration-dependent and competitive manner with a KB value of 5.01 nm. Also reversed by SCH58261 (60 nmol/L) were the increases in coronary conductance caused by the relatively selective A1AdoR agonists CCPA (70 nM), and (R)-(-)N(b)-(2-phenyl-isopropyl)**adenosine** (60 nM) but not those caused by sodium nitroprusside (1.2 microM) and diltiazem (0.4 microM). SCH58261 (< or = 100 nM) did not attenuate the A1AdoR-mediated prolongations of S-H interval caused by either **adenosine** or CCPA. SCH58261 attenuated the coronary vasodilation caused by 50 nM **adenosine** with an IC50 value of 6.8 +/- 0.6 nM. The coronary vasodilations caused by the nucleoside uptake inhibitor draflazine and the **adenosine** kinase inhibitor iodotubercidin were completely reversed by 60 nM SCH58261 or **adenosine** deaminase (7 U/ml). Thus, the A2AAdoR plays a major role as mediator of coronary vasodilation caused by exogenous and endogenous **adenosine** and by AdoR agonists.

2/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09667707 98119654 PMID: 9459566
Comparative pharmacology of human **adenosine** receptor subtypes - characterization of stably transfected receptors in CHO cells.
Klotz KN; Hessling J; Hegler J; Owman C; Kull B; Fredholm BB; Lohse MJ
Institut fur Pharmakologie und Toxikologie, Universitat Wurzburg, Germany.
Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Jan 1998, 357 (1) p1-9, ISSN 0028-1298 Journal Code: NTQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Four **adenosine** receptor subtypes of the family of G protein-coupled receptors, designated A1, A2A, **A2B** and A3 are currently known. In this study all human subtypes were stably transfected into Chinese hamster ovary (CHO) cells in order to be able to study their pharmacological profile in an identical cellular background utilizing radioligand binding studies (A1, A2A, A3) or adenylyl cyclase activity assays (**A2B**). The A1 subtype showed the typical pharmacological profile with 2-chloro-N6-cyclopentyladenosine (CCPA) as the agonist with the highest affinity and a marked stereoselectivity for the N6-phenylisopropyladenosine (PIA) diastereomers. In competition with **antagonist** radioligand biphasic curves were observed for agonists. In the presence of GTP all receptors were converted to a single low affinity state indicating functional coupling to endogenous G proteins. For A2A **adenosine** receptors CGS 21680 (2-[p-(2-carboxyethyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine) and N-ethylcarboxamidoadenosine (NECA) were found to be the most potent agonists followed by R- and S-PIA with minor stereoselectivity. The relative potencies of agonists for the **A2B** **adenosine** receptor could only be tested by measurement of receptor-stimulated adenylyl cyclase activity. NECA was the most potent agonist with an EC50-value of 2.3 microM whereas all other compounds tested were active at concentrations in the high micromolar range. Inhibition of NECA-stimulated adenylyl cyclase identified xanthine amino congener (XAC; 8-[4-[[[(2-aminoethyl)amino]-carbonyl]methyl]oxy]phenyl]-1,3-dipropylxa

nthine) as the most potent **antagonist** at this receptor subtype. The A3 receptor was characterized utilizing the nonselective agonist [3H]NECA. The N6-benzyl substituted derivatives of **adenosine** -5'-N-methyluronamide (MECA) turned out to be the most potent agonists. The notion of xanthine-insensitivity of the A3 receptor should be dropped at least for the human receptor as xanthines with submicromolar affinity were found. Overall, the pharmacological characteristics of the human receptors are similar to other species with some species-specific characteristics. In this study we present for the first time the comparative pharmacology of all known human **adenosine** receptor subtypes. The CHO cells with stably transfected **adenosine** receptors provide an identical cellular background for such a pharmacological characterization. These cells are valuable systems for further characterization of specific receptor subtypes and for the development of new ligands.

2/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09652883 98114100 PMID: 9453355
Adenosine inhibits growth of human aortic smooth muscle cells via **A2B** receptors.
Dubey RK; Gillespie DG; Mi Z; Jackson EK
Department of Medicine, University of Pittsburgh Medical Center, PA 15213-2582, USA. dubey@novell2.dept-med.pitt.edu
Hypertension (UNITED STATES) Jan 1998, 31 (1 Pt 2) p516-21, ISSN 0194-911X Journal Code: GK7
Contract/Grant No.: HL 35909, HL, NHLBI; HL 55314, HL, NHLBI
Language: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine inhibits rat vascular smooth muscle cell (SMC) growth. However, the effects of **adenosine** on human vascular SMC proliferation and synthesis of extracellular matrix proteins, such as collagen, are unknown. The objective of this study was to characterize the effects of exogenous and endogenous (SMC-derived) **adenosine** on human aortic SMC proliferation and collagen synthesis. Growth-arrested SMCs were stimulated with 2.5% fetal calf serum (FCS) in the presence and absence of **adenosine**, 2-chloroadenosine (stable **adenosine** analogue), and with agents that increase endogenous **adenosine** levels, including erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), dipyridamole, and iodotubericidin. All of these agents inhibited in a concentration-dependent manner FCS-induced SMC proliferation as assessed by DNA synthesis (3H-thymidine incorporation) and cell counting, as well as collagen synthesis (3H-proline incorporation). EHNA, dipyridamole, and iodotubericidin increased extracellular levels of **adenosine** by 1.7-fold to 18-fold when added separately to SMCs, and EHNA+iodotubericidin and EHNA+iodotubericidin+dipyridamole increased extracellular **adenosine** levels by more than 392-fold. Both KF17837 (selective A2 **antagonist**) and DPSPX (A1/A2 **antagonist**), but not DPCPX (selective A1 **antagonist**), blocked the antimitogenic effects of 2-chloroadenosine, EHNA, and dipyridamole on DNA and collagen synthesis, suggesting the involvement of A2A and/or **A2B**, but excluding the participation of A1, receptors. The lack of effect of CGS21680 (selective A2A agonist), excluded involvement of A2A receptors and suggested a major role for **A2B** receptors. A comparison of the inhibitory potencies of 2-chloroadenosine, N6-cyclopentyladenosine (selective A1 agonist), NECA (A1/A2 agonist), and MECA (A1/A2 agonist) were consistent with an **A2B** receptor subtype mediating the inhibitory effects of **adenosine** on human aortic SMC proliferation. In conclusion, human aortic SMCs synthesize **adenosine**, and exogenous as well as endogenous (SMC-derived) **adenosine** inhibits SMC proliferation and collagen synthesis via activation of **A2B** receptors.

2/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09652852 98114064 PMID: 9453319
Cyclic AMP-**adenosine** pathway induces nitric oxide synthesis in aortic smooth muscle cells.
Dubey RK; Gillespie DG; Jackson EK
Department of Medicine, University of Pittsburgh Medical Center, Pa 15213-2582, USA. dubey@novell2-dept-med.pitt.edu
Hypertension (UNITED STATES) Jan 1998, 31 (1 Pt 2) p296-302, ISSN 0194-911X Journal Code: GK7
Contract/Grant No.: HL 35909, HL, NHLBI; HL 55314, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The main purpose of this investigation was to evaluate whether the cyclic AMP-**adenosine** pathway, ie, the conversion of cAMP to AMP and, hence, to **adenosine**, is involved in the regulation of nitric oxide (NO) synthesis by vascular smooth muscle cells (SMCs). Treatment of confluent monolayers of SMCs with **adenosine**, 2-chloroadenosine (stable analog of **adenosine**), and agents that elevate endogenous (SMC-derived) **adenosine** (EHNA and iodotubericidin) increased nitrite/nitrate (stable metabolites of NO) levels in the medium and enhanced the conversion of 3H-L-arginine to 3H-L-citrulline by cytosolic extracts obtained from the pretreated SMCs. The stimulatory effects of **adenosine** were not mimicked by low (1 to 100 nmol/L) concentrations of CGS21680, an A2A receptor agonist, or CPA, a selective A1 receptor agonist. The stimulatory effects of 2-chloroadenosine and EHNA plus iodotubericidin were significantly inhibited by KF17837, a selective A2 receptor **antagonist**, and by DPSPX, an A1/A2 receptor **antagonist**, but not by DPCPX, a selective A1 receptor **antagonist**. DDA (adenylyl cyclase inhibitor) and Rp-cyclic AMP (protein kinase A inhibitor) did not block the effects of **adenosine** on NO synthesis. Incubation of SMCs with exogenous cyclic AMP, at concentrations previously shown to elevate levels of**adenosine** in the medium, also increased nitrite/nitrate levels and 3H-L-citrulline formation, and the effects of cyclic AMP on NO synthesis were blocked by DPSPX and KF17837, but not by DPCPX. These findings provide evidence that exogenous and SMC-derived **adenosine** induce NO synthesis via **A2B** receptors linked to a pathway not involving adenylyl cyclase/protein kinase A. Moreover, extracellular cyclic AMP induces NO synthesis via conversion to **adenosine** and activation of **A2B** **adenosine** receptors. The cyclic AMP-**adenosine** pathway may be importantly involved in the vascular production of NO.

2/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09630815 98004319 PMID: 9346333
Relaxation of the ovine isolated iris sphincter by **adenosine** receptor agonists: lack of effect of **adenosine** A1 and A2 receptor antagonists.
Hourani SM; Smith NC; Nettell JJ; Hall JM
School of Biological Sciences, University of Surrey, Guildford, UK. s.hourani@surrey.ac.uk
European journal of pharmacology (NETHERLANDS) Sep 3 1997, 334 (1) p95-8, ISSN 0014-2999 Journal Code: EN6
Language: ENGLISH
Document type: Journal Article
Record type: Completed
The effects of **adenosine** receptor ligands on the tone of the ovine isolated iris sphincter were investigated, and **adenosine** analogues were found to relax the carbachol-contracted tissue in a concentration-dependent manner with an order of potency of 5'-N-ethylcarboxamidoadenosine > or = 2-(p-(2-carboxyethyl)phenylethylamino

)-5'-N-ethylcarboxamidoadenosine (CGS 21680) > or = N6-cyclopentyladenosine **adenosine**, consistent with activation of an **adenosine** A2A receptor. However, these responses were not inhibited by the non-selective **adenosine** A1/A2 receptor **antagonist** 8-p-sulphophenyltheophylline (50 microM), the selective **adenosine** A2A/A1 receptor **antagonist** N-[2-(dimethylamino)ethyl]-N-methyl-4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3- dipropyl-1H-purin-8-yl)benzenesulphonamide (PD 115,199) (0.1 microM) or the non-xanthine **adenosine** A2A receptor **antagonist** (4-(2-[7-amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl-amino]ethyl)phenol) (ZM 241385) (0.1 microM). The relaxations cannot therefore be mediated by activation of **adenosine** A1, A2A or **A2B** receptors.

2/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

00629018 98081656 PMID: 9421303
Activation of two sites by **adenosine** receptor agonists to cause relaxation in rat isolated mesenteric artery.
Prentice DJ; Payne SL; Hourani SM
School of Biological Sciences, University of Surrey, Guildford.
British journal of pharmacology (ENGLAND) Dec 1997, 122 (7) p1509-15
, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. In this study we have characterized the receptor(s) in the rat mesenteric artery mediating relaxant responses to **adenosine** and a number of **adenosine** analogues, N6-R-phenylisopropyladenosine (R-PIA), N6-cyclopentyladenosine (CPA), N6-(3-iodo-benzyl)-**adenosine**-5'-N-methyluronamide (IB-MECA) and 5'-N-ethylcarboxamidoadenosine (NECA), by use of the non-selective **antagonist** 8-sulphophenyltheophylline (8-SPT) and the A2A selective ligands 2-[p-(2-carbonylethyl)-phenylethylamino]-5'-N-ethylcarboxamidoadenosine (CGS 21680) and 4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]-triazin-5- ylamino]ethyl) phenol (ZM 241385). We have also studied the effects of endothelial removal and uptake inhibition by nitrobenzylthioinosine (NBTI) and the effects of the A3 receptor **antagonist** 1,3-dipropyl-8-(4-acrylate)phenylxanthine (BWA1433). 2. **Adenosine**, NECA, CPA and R-PIA all elicited relaxant responses in tissues precontracted with phenylephrine (1 microM) with the following potency order: NECA > R-PIA > **adenosine** = CPA. However, E/[A] curves to NECA were biphasic. CGS 21680 was inactive at concentrations up to 30 microM and IB-MECA elicited relaxant responses which were resistant to blockade by 8-SPT and BWA1433 (100 microM). 3. Removal of the endothelium produced a small but significant decrease in the asymptote of the high potency phase of E/[A] curves to NECA with no change in p[A]50. E/[A] curves to **adenosine** were not altered by removal of the endothelium. However, there were small rightward shifts of E/[A] curves to CPA and R-PIA in the absence of endothelium. 4. Inhibition of uptake by NBTI (1 microM) had no effect on E/[A] curves to NECA, CPA or R-PIA, but E/[A] curves to **adenosine** were significantly left-shifted in the presence of NBTI. 5. 8-SPT (10-100 microM) caused significant rightward shifts of the high potency phase of the E/[A] curves to NECA (pA2 = 5.63+/-0.26). The second phase of the concentration-response curve to NECA appeared to be resistant to blockade by 8-SPT, as were E/[A] curves for **adenosine**, CPA or R-PIA. However, in the presence of NBTI (1 microM), 8-SPT (100 microM) gave significant rightward shifts of E/[A] curves to **adenosine**. 6. ZM 241385 (0.1-1 microM) produced significant rightward shifts of the high potency phase of NECA E/[A] curves (pA2=7.65+/-0.25 in the presence and 7.20+/-0.11 in the absence of endothelium), while curves to R-PIA were not significantly shifted by 1 microM ZM 241385. In the presence of NBTI E/[A] curves to **adenosine** were significantly rightward shifted by ZM 241385 (0.1 microM, pA2=7.50+/-0.16). 7. In conclusion, the results suggest activation of **A2B** receptors located primarily on the smooth muscle by

low concentrations of NECA and by **adenosine** under conditions of uptake blockade, and another, as yet undefined site which may be intracellular, by higher concentrations of NECA, by CPA, R-PIA and **adenosine** under conditions where uptake is operational.

2/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09604[illegible] 98068823 PMID: 9406988
Use of a newly developed technique to isolate rat pinealocytes and study the effects of **adenosine** agonists on melatonin production.
Nicholls J; Skene DJ; Hourani SM
School of Biological Sciences, University of Surrey, Guildford, United Kingdom. j.boyle@surrey.ac.uk
Journal of pineal research (DENMARK) Oct 1997, 23 (3) p164-8, ISSN 0742-3098 Journal Code: JND
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Recent studies have suggested a role for **adenosine** in the regulation of rat pineal melatonin synthesis. The data, however, are conflicting and therefore the aim of this study was to characterize **adenosine** receptors more fully in vitro by using a range of selective **adenosine** agonists and the **adenosine antagonist** 8-sulphophenyltheophylline (8-SPT). A simple method for the mechanical separation of rat pinealocytes was developed. Pinealocytes were briefly (15 min) incubated with drugs followed by a 4 hr drug-free incubation period after which melatonin concentrations in the incubation medium were measured by radioimmunoassay. The beta-adrenoceptor agonist isoprenaline gave a dose-related increase in melatonin production, demonstrating that this pinealocyte preparation technique is suitable to evaluate the effect of drugs on pineal melatonin synthesis. Our results show that **adenosine**, N6-(phenylisopropyl)**adenosine** (R-PIA) and 2-p-(2-carboxethyl) phenethylamino-5'-N-ethylcarboxamidoadenosine (CGS21680) did not affect melatonin synthesis alone or in combination with isoprenaline. However 5'-N-ethylcarboxamidoadenosine (NECA) (100 microM) potentiated the stimulatory effect of isoprenaline (3 microM) on pineal melatonin production and this effect appeared to be antagonized by 8-SPT (50 microM). These results are consistent with activation by NECA of an **A2b adenosine** receptor.

2/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09561273 97426233 PMID: 9282937
Stimulation of interleukin-6 secretion and gene transcription in primary astrocytes by **adenosine**.
Schwaninger M; Neher M; Viegas E; Schneider A; Spranger M
Department of Neurology, University of Heidelberg, Germany.
Journal of neurochemistry (UNITED STATES) Sep 1997, 69 (3) p1145-50, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
During cerebral ischemia, the expression of interleukin-6 (IL-6), which has neuroprotective properties, increases. To understand the underlying mechanism, the regulation of IL-6 expression by neurotransmitters that accumulate during cerebral ischemia was investigated. **Adenosine** stimulated IL-6 secretion in primary astrocytes four- to 10-fold. The effect was concentration dependent, the EC50 being approximately 8 microM. Although the nonselective analogue 2-chloroadenosine (2CA) increased IL-6 secretion to a similar extent, the A1-selective agonist N6-cyclopentyladenosine or the A2a agonist CGS-21680 had only a marginal

effect on IL-6 secretion. IL-6 secretion stimulated by 2CA (10 microM) was inhibited by the nonselective **adenosine antagonist** 8-(p-sulfophenyl)theophylline, whereas the A1-selective **antagonist** 8-cyclopentyl-1,3-dipropylxanthine or the A2a-selective **antagonist** 8-(3-chlorostyryl)caffeine had no effect, to a concentration of 0.1 microM. Transcription of the IL-6 gene was investigated by transfecting primary astrocytes with a reporter fusion gene containing the human IL-6 promoter (-179/+12). 2CA stimulated IL-6 gene transcription 2.5-fold. Mutations of the binding site for NF-kappaB or NF-IL6 abrogated the response to 2CA. Thus, an increase of extracellular **adenosine** during focal cerebral ischemia may stimulate IL-6 expression via **A2b** receptors. The induction of IL-6 expression appears to involve a transcriptional effect that depends on NF-kappaB and NF-IL6.

2/3,AB 49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

094910** 95134624 PMID: 7833226
Adenosine modulation of neurotransmission in penile erection.
Chiang PH; Wu SN; Tsai EM; Wu CC; Shen MR; Huang CH; Chiang CP
Department of Urology, Kaohsiung Medical College, Taiwan, ROC.
British journal of clinical pharmacology (ENGLAND) Oct 1994, 38 (4) p357-62, ISSN 0306-5251 Journal Code: AU9
Languages: ENGLISH
Document type: Clinical Trial; Journal Article
Record type: Completed
1. **Adenosine** inhibited the noradrenaline-induced contraction of rabbit corpus cavernosum in a dose-dependent manner. The effect of **adenosine** was greater in intact corpus cavernosa than in endothelium-denuded preparations. This finding indicates that the relaxing effect of **adenosine** is partially endothelium-dependent and involved in the release of endothelium-derived relaxing factors. 2. **Adenosine** and its analogues relaxed the noradrenaline-induced contractile response as well as inhibited the transmural nerve induced contraction with the potency order: NECA > R-PIA > **adenosine**. These data indicate that **adenosine** can modulate both the non-adrenergic non-cholinergic and adrenergic neurotransmission. DMPX, an **adenosine antagonist** selective for the A2 receptors, abolished the electrically elicited relaxation. However, CGS 21680, selective for A2a receptor, had no effect on relaxation. Therefore, **adenosine** receptors involved in the modulation of neurotransmission in rabbit corpus cavernosum appear to be **A2b** subtype. 3. **Adenosine** also induced an increase in human cavernosal arterial velocity and resistive index measured by colour duplex sonography. The combination of **adenosine** and 10 micrograms prostaglandin E1 was more effective in resistive index and erection grade than 20 micrograms prostaglandin E1 alone. Our results suggest that **adenosine** seems to be an important neuromodulator for penile erection and can be an effective and alternative combination in the treatment of impotence.

2/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09480110 98026625 PMID: 9362302
A1 **adenosine** receptors potently regulate heart rate in mammalian embryos.
Hoffman PL; Hiatt K; Yoder MC; Rivkees SA
Section of Pediatric Endocrinology, Herman B. Wells Center for Pediatric Research, James Whitcomb Riley Hospital, Indianapolis, Indiana 46202, USA.
American journal of physiology (UNITED STATES) Oct 1997, 273 (4 Pt 2) pR1374-80, ISSN 0002-9513 Journal Code: 3U8
Contract/Grant No.: HL-58442, HL, NHLBI
Languages: ENGLISH

Document type: Journal Article
Record type: Completed

A1 **adenosine** receptors (A1ARs) have been recently shown to be expressed in rodent embryonic hearts at very early stages of development. To determine the functional significance of fetal cardiac A1AR expression during embryogenesis, murine fetal heart preparations were studied between postconceptual days 9 and 12. Dose-response curves generated using a variety of **adenosine** agonists revealed that A1AR activation potently regulated fetal heart rates. The A1AR agonist, N6-cyclopentyladenosine, inhibited heart rates in a dose-dependent manner (half-maximal effective concentration = 3.6 x 10(-8) M) and stopped fetal cardiac contractions in 63% of preparations. In contrast, A2a and **A2b** receptor activation did not alter heart rates, and activation of A3 receptors produced modest declines in heart rates. Endogenous **adenosine** also acted tonically to suppress fetal heart rates, as demonstrated by the A1AR **antagonist** 1,3-dipropyl-8-cyclopentylxanthine, increasing heart rates, whereas the **adenosine** reuptake blocker dipyridamole lowered fetal heart rates. Pertussis toxin treatment blocked A1AR action, showing that A1AR action was G protein mediated. Using drugs that alter cAMP levels and ion channel action, we were able to show that A1AR action involves events mediated by cAMP, ATP-dependent K, L-type calcium, sodium, and chloride channels, and the pacemaker current. These data show that **adenosine** and A1ARs potently regulate mammalian heart rates via multiple effector systems at very early stages of prenatal development.

2/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09443400 98015984 PMID: 9355907

Exogenous and endogenous **adenosine** inhibits fetal calf serum-induced growth of rat cardiac fibroblasts: role of **A2B** receptors.

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Circulation (UNITED STATES) Oct 21 1997, 96 (8) p2656-66, ISSN 0009-7322 Journal Code: DAW

Contract Grant No.: HL-35909, HL, NHLBI; HL-55314, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

BACKGROUND: Because proliferation of cardiac fibroblasts participates in cardiac hypertrophy/remodeling associated with hypertension and myocardial infarction, it is important to elucidate factors regulating cardiac fibroblast proliferation. **Adenosine**, a nucleoside abundantly produced by cardiac cells, is antimitogenic vis-a-vis vascular smooth muscle cells; however, the effect of **adenosine** on cardiac fibroblast proliferation is unknown. The objective of this study was to characterize the effects of exogenous and endogenous (cardiac fibroblast-derived) **adenosine** on cardiac fibroblast proliferation. METHODS AND RESULTS: Growth-arrested cardiac fibroblasts were stimulated with 2.5% FCS in the presence and absence of **adenosine**, 2-chloroadenosine (stable **adenosine** analogue), or modulators of **adenosine** levels, including (1) erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA; **adenosine** deaminase inhibitor); (2) dipyridamole (**adenosine** transport blocker); and (3) iodotubericidin (**adenosine** kinase inhibitor). All of these agents inhibited, in a concentration-dependent manner, FCS-induced cardiac fibroblast proliferation as assessed by DNA synthesis ([3H]thymidine incorporation) and cell counting. EHNA, dipyridamole, and iodotubericidin increased extracellular levels of **adenosine** by 2.3- to 5.6-fold when added separately to cardiac fibroblasts, and EHNA+iodotubericidin or EHNA+iodotubericidin+dipyridamole increased extracellular **adenosine** levels by >690-fold. Both KF17837 (selective A2 **antagonist**) and DPSPX (nonselective A2 **antagonist**) but not DPCPX (selective A1

antagonist) blocked the antimitogenic effects of 2-chloroadenosine, EHNA, and dipyridamole on DNA synthesis, suggesting the involvement of A2A and/or **A2B** but excluding the participation of A1 receptors. The lack of effect of CGS21680 (selective A2A agonist) excluded involvement of A2A receptors and suggested a major role for **A2B** receptors. This conclusion was confirmed by the rank order potencies of four **adenosine** analogues. CONCLUSIONS: Cardiac fibroblasts synthesize **adenosine**, and exogenous and cardiac fibroblast-derived **adenosine** inhibits cardiac fibroblast proliferation via activation of **A2B** receptors. Cardiac fibroblast-derived **adenosine** may regulate cardiac hypertrophy and/or remodeling by modulating cardiac fibroblast proliferation.

2/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09418975 98020729 PMID: 9378250
Involvement of functional antagonism in the effects of **adenosine** antagonists and L-NAME in the rat isolated heart.
Lewis CD; Hourani SM
School of Biological Sciences, University of Surrey, Guildford, United Kingdom.
General pharmacology (ENGLAND) Sep 1997, 29 (3) p421-7, ISSN 0306-3623 Journal Code: FLK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. **Adenosine** and its analogues induced an increase in flow rate when infused into the rat isolated perfused heart. The agonist potency order obtained was 2-(rho-(2-carboxyethyl)phenethyl-amino)-5'-N-ethylcarboxamidoadenosine (CGS 21680) > or = 5'-N-ethylcarboxamidoadenosine (NECA) > N6-cyclopentyladenosine = **adenosine** , although the maximal response obtained for CGS 21680 was only 70% of that achieved by NECA. NG-Nitro-L-arginine methyl ester (L-NAME), the nonselective **adenosine** **antagonist** 8-rho-(sulfophenyl)theophylline (8-SPT) and the A2a selective **antagonist** N-[2-(dimethylamino)ethyl]-N-methyl-4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3- diprophyl-1H-purin-8-yl)benzene sulfonamide (PD 115, 199) reduced responses to the **adenosine** agonists, but some of this reduction was shown to be due to a nonspecific decrease in flow rate as well as a specific inhibitory action. 2. When this functional antagonism is taken into account, the results suggest that the increase in flow rate induced by the **adenosine** agonists was mediated by A2 receptors, with the increase in flow rate induced by CGS 21680 mediated by A2a receptors, whereas that induced by NECA was mediated by **A2b** receptors. 3. L-NAME did not appear to have any effect on the increase in flow rate induced by the **adenosine** agonists, suggesting that these responses were probably endothelium independent and do not involve the nitric oxide pathway.

2/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09401827 97259785 PMID: 9105884
Adenosine analogues relax guinea-pig taenia caeci via an **adenosine A2B** receptor and a xanthine-resistant site.
Prentice DJ; Hourani SM
School of Biological Sciences, University of Surrey, Guildford, UK.
European journal of pharmacology (NETHERLANDS) Mar 26 1997, 323 (1) p103-6, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In this study we have sub-classified the **adenosine** A2 receptor mediating relaxation in the guinea-pig taenia caecum using the

adenosine A2A receptor-selective agonist CGS 21680 (2-[p-(2-carboxyethyl)phenylamino]-5'-N-ethylcarboxamidoadenosine) and the **adenosine** A2A receptor-selective **antagonist** ZM 241385 (4-(2-[7-amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl amino]ethyl)phenol). CGS 21680 did not elicit relaxations, and a pKB value of 7.80 was obtained for ZM 241385 against 5'-N-ethylcarboxamidoadenosine suggesting the presence of **adenosine A2B** receptors. Relaxations are also mediated via a xanthine-resistant site. In this study relaxations to the **adenosine** A3 receptor agonist IB-MECA (N6-(3-iodo-benzyl) **adenosine** -5'-N-methyluronamide) were blocked by neither 8-sulphophenyltheophylline (100 microM) nor the **adenosine** A3 receptor **antagonist** BW-A1433 (1,3-dipropyl-8-(4-acrylate)phenylxanthine, 100 microM), suggesting that this site is not an **adenosine** A3 receptor.

2/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09384042 97130896 PMID: 9187331

A role for **adenosine** A2 receptors in the induction of long-term potentiation in the CA1 region of rat hippocampus.

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Brain research (NETHERLANDS) May 9 1997, 756 (1-2) p184-90, ISSN 0006-8993 Journal Code: B5L

Contract/Grant No.: NS01498, NS, NINDS; NS31764, NS, NINDS

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Document type: Journal Article

Record type: Completed

Although reductions in neurotransmission have been reported in response to agonist-mediated **adenosine** A1 receptor activation, the implications of A2 receptor activation on synaptic transmission have not been well explored. We examined the role **adenosine** A2 receptors play in the efficacy of neurotransmission between the Schaffer collateral-CA1 pathway in the rat transverse hippocampal slice. A2 receptor blockade in the presence of complete A1 receptor inhibition led to a reversible reduction of the field excitatory post-synaptic potential (EPSP) slope in response to low-frequency test pulses (0.033 Hz) indicating that A2 receptors can enhance synaptic transmission. A2 receptor blockade by the A2 **antagonist** , DMPX (3,7-dimethyl-1-propargylxanthine) prevented the induction of tetanus-induced long-term potentiation (LTP) of the EPSP. In contrast, no such effect on LTP induction was observed during A1 receptor blockade. We also examined the effects of DMPX on the induction of LTP during continued A1 receptor blockade with CPT. Under this condition, LTP was significantly reduced when compared to LTP induced in the presence of CPT alone. A similar result was found using the highly polar A2 **antagonist** 8-SPT (8-(p-sulfophenyl)theophylline) suggesting that the effects of DMPX on LTP were not due to a direct action on an intracellular intermediate. DMPX had no effect on LTP expression if applied 45 min following the tetanus indicating that A2 receptors play no significant role in the maintenance phase of LTP. Selective A2a receptor activation did not alter the field EPSP. Similarly, selective blockade of the A2a receptor did not interfere with tetanus-induced LTP. Increases in neuronal firing rates can result in elevations in the concentration of extracellular **adenosine** . Together, these results suggest that the A2 receptors may play an important role in the induction although not the maintenance of hippocampal LTP and that the effect is likely to be mediated by the **A2b** receptor.

2/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09204902 97278083 PMID: 9131417

P1-purinoceptor-mediated vasodilatation and vasoconstriction in hypoxia.
Broadley KJ; Maddock R[redacted]
Department of Pharmacology, Welsh School of Pharmacy, University of Wales Cardiff, UK.
Journal of autonomic pharmacology (ENGLAND) Dec 1996, 16 (6) p363-6, ISSN 0144-1795 Journal Code: HJG
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The effects of **adenosine** receptor agonists were examined on isolated rings of guinea-pig pulmonary artery under normoxic and hypoxic conditions. The rings were denuded of endothelium and tissues were precontracted with phenylephrine (3 x 10(-6) M) before constructing cumulative concentration-response curves to the agonists. 2. 5'-(N-ethylcarboxamido)**adenosine** (NECA) caused concentration-dependent contractions of the pulmonary artery which were not different between hypoxia and normoxia. The contractions were converted to a relaxation in the presence of the cyclooxygenase inhibitor, indomethacin, and again these were unaffected by hypoxia. 3. Examination of a range of agonists under normoxic conditions in the presence of indomethacin revealed relaxations, except for the A2a receptor-selective agonist, CGS 21680. The vasorelaxation was therefore **A2b** receptor-mediated. 4. In hypoxia, however, in the presence of indomethacin, vasoconstriction occurred to R(-)-N(6)-(2-phenylisopropyl)**adenosine** (R-PIA) and, to a greater extent, to N6-cyclopentyladenosine (CPA). In the absence of indomethacin, the constriction by CPA during hypoxia was significantly greater. 5. The indomethacin-resistant contraction by CPA was abolished by the A1 receptor **antagonist**, 8-cyclopentyltheophylline (CPT, 3 x 10(-6) M). 6. This study has demonstrated cyclooxygenase-dependent and-independent vasoconstrictions to **adenosine** agonists in guinea-pig pulmonary artery under hypoxic conditions. The cyclooxygenase-independent contraction is mediated via A1 receptors. 7. These results suggest that endogenous **adenosine** released in the pulmonary circulation under hypoxic conditions will cause vasoconstriction and may contribute to the pulmonary hypertension associated with acute respiratory failure.

2/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09201429 97070852 PMID: 8913778
Cyclooxygenase-2 expression in rat microglia is induced by **adenosine** A2a-receptors.
Fiebich BL; Biber K; Lieb K; van Calker D; Berger M; Bauer J; Gebicke-Haerter PJ
Abt. Psychiatrie, Universitat Freiburg, Germany.
Glia (UNITED STATES) Oct 1996, 18 (2) p152-60, ISSN 0894-1491 Journal Code: GLI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We investigated the regulation of COX-2 expression and activity by **adenosine** receptors in rat microglial cells. The selective **adenosine** A2a-receptor agonist CGS21680 and the non-selective **adenosine** A1- and A2-receptor agonist 5'-N-ethylcarboxiamidoadenosine (NECA) induced an increase in COX-2 mRNA levels and the synthesis of prostaglandin E2 (PGE2). The **adenosine** A1-receptor agonist cyclopentyladenosine (CPA) was less potent, and the **adenosine** A1-receptor-specific agonist N6-2-(-aminophenylo)ethyladenosine (APNEA) showed only marginal effects. Microglia expressed **adenosine** A1-, A2a-, and A3-, but not **A2b**-receptor mRNAs, whereas astroglial cells expressed **adenosine** **A2b**- but not A2a-receptor mRNA. The **adenosine** A2a-receptor selective **antagonist** (E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine (KF17837) inhibited both CGS21680-induced COX-2 expression and PGE2 release. CGS21680-increased PGE2

levels were inhibited by dexamethasone, by the nonsteroidal antiinflammatory drug [redacted]oxicam, and by the adenylyl cyclase inhibitor 9-(tetrahydro-2-furanyl)-9H-purine-6-amine (SQ22536). CGS21680 and NECA both increased intracellular cAMP levels in microglial cells. Dibutyryl cAMP as well as forskolin induced the release of PGE2. The results strongly suggest that **adenosine** A2a-receptor-induced intracellular signaling events cause an up-regulation of the COX-2 gene and the release of PGE2. Apparently, the cAMP second messenger system plays a crucial role in COX-2 gene regulation in rat microglial cells. The results are discussed with respect to neurodegenerative disorders of the CNS such as Alzheimer's disease, in which activated microglia are critically involved and COX inhibitors may be of therapeutic benefit.

2/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09187574 96348125 PMID: 8761029
Modulation of erythropoietin production by selective **adenosine** agonists and antagonists in normal and anemic rats.
Nagashima K; Karasawa A
Department of Pharmacology, Kyowa Hakko Kogyo Co., Ltd., Shizuoka, Japan.
Life sciences (ENGLAND) 1996, 59 (9) p761-71, ISSN 0024-3205 Journal Code: L62
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Hypoxia or anemia is the fundamental stimulus for erythropoietin (EPO) production. Recent in vitro studies suggest that EPO secretion in response to hypoxia is regulated by **adenosine** in the kidney. In order to examine the in vivo effect of **adenosine** on EPO production, we determined the effects of **adenosine** receptor agonists and antagonists on serum EPO concentration in normal and anemic rats. In normal rats, intravenous injection of **adenosine** agonists (NECA, CHA and CGS-21680) dose-dependently stimulated EPO production. Pretreatment with KW-3902, an **adenosine** A1 **antagonist** with modest **A2b** antagonistic action, or KF17837, an **adenosine** A2a **antagonist**, inhibited the NECA (0.1 mg/kg, i.v.)-stimulated EPO production. Anemic hypoxia, induced by 2% (v/w body weight) blood withdrawal, increased serum EPO concentration from 38 +/- 3 to 352 +/- 76 mU/ml, with the increased serum **adenosine** concentration in the renal vein. KF17837 (0.1 mg/kg, i.v.), but not KW-3902 (0.1 mg/kg, i.v.), inhibited the anemic hypoxia-induced increase in EPO production. The present findings support the notion that **adenosine** mediates the EPO production in response to hypoxia in the kidney.

2/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09185713 96250451 PMID: 8692279
Functional characterization of **adenosine** A2 receptors in Jurkat cells and PC12 cells using **adenosine** receptor agonists.
van der Ploeg I; Ahlberg S; Parkinson FE; Olsson RA; Fredholm BB
Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Feb 1996, 353 (3) p250-60, ISSN 0028-1298 Journal Code: NTQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The effect of several **adenosine** analogues on cyclic AMP accumulation was examined in the rat phaeochromocytoma cell PC12 and in the human T-cell leukaemia cell Jurkat, selected as prototypes of cells predominantly expressing **adenosine** A2A or **A2B** receptors. Using the reverse transcription-polymerase chain reaction it was, however,

demonstrated that the Jurkat cell and the PC12 cell express both A2A and **A2B** receptor mRNA, albeit in different relative proportions. In PC12 cells the concentration required for half-maximal response (EC50) for the full agonist 5'-N-ethyl-carboxamidoadenosine (NECA) was 30 times lower than in Jurkat cells. There was no significant difference in the pA2 for the **antagonist** 5-amino-9-chloro-2-(2-furanyl)- 1,2,4-triazolo(1,5-C)quina zolinemonomethanesulphonate (CGS 15943) between the two cell types. In the presence of forskolin (1 microM in PC12 cells; 10 microM in Jurkat cells) the EC50 value for NECA was reduced two-to sixfold. Forskolin also increased the maximal cAMP accumulation twofold in PC12 cells and sevenfold in Jurkat cells. A series of 2-substituted **adenosine** analogues CV 1808 (2-phenylamino **adenosine**), CV 1674 [2-(4-methoxyphenyl) **adenosine**], CGS 21680 2-[p-(2-carbonylethyl)phenylethylamino]-5'-N-et hyl- carboxamido **adenosine** , and four 2-substituted isoguanosines, SHA 40 [2-(2-phenylethoxy)**adenosine** ; PEA], SHA 91 [2-(2-cyclohexylethoxy)**adenosine**; CEA], SHA 118 2-[2-(p-methylphenyl) ethoxy]**adenosine** ; MPEA , and SHA 125 (2-hexyloxyadenosine; HOA), all raised cAMP accumulation in PC12 cells, but had minimal or no effect in Jurkat cells. In the PC12 cells the addition of forskolin (1 microM) reduced the EC50 by a factor of 2(CV 1808) to 12 (SHA 125). In Jurkat cells all the analogues gave a significant, but submaximal, cAMP response in the presence of forskolin (10 microM), but they were essentially inactive in its absence. The results show that a series of 2-substituted **adenosine** analogues can be used to discriminate between A2A and **A2B** receptors. The two receptor subtypes appear to coexist, even in clonal cells selected for typical pharmacology. A2 receptor pharmacology can therefore be complex.

2/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09181431 97137367 PMID: 8982704

Adenosine A2A receptors modulate the binding characteristics of dopamine D2 receptors in stably cotransfected fibroblast cells.

Dasgupta S; Ferre S; Kull B; Hedlund PB; Finnman UB; Ahlberg S; Arenas E; Fredholm BB; Fuxe K

Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden.

European journal of pharmacology (NETHERLANDS) Dec 5 1996, 316 (2-3) p325-31, ISSN 0014-2999 Journal Code: EN6

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

In membrane preparations from rat striatum, where **adenosine** A2A and dopamine D2 receptors are coexpressed, stimulation of **adenosine** A2A receptors was found to decrease the affinity of dopamine D2 receptors for dopamine agonists. We now demonstrate the existence of this antagonistic interaction in a fibroblast cell line (Ltk-) stably transfected with the human dopamine D2 (long-form) receptor and the dog **adenosine** A2A receptor cDNAs (A2A-D2 cells). In A2A-D2 cells, but not in control cells only containing dopamine D2 receptors (D2 cells), the selective **adenosine** A2A agonist 2-[p-(2-carboxyethyl)-phenethylamino]-5'-N-ethy l-carboxamido **adenosine** (CGS 21680) induced a 2-3-fold decrease in the affinity of dopamine D2 receptors for dopamine, as shown in competition experiments with dopamine versus the selective dopamine D2 **antagonist** [3H]raclopride. By contrast, activation of the constitutively expressed **adenosine** **A2B** receptors with 5'-N-ethyl-carboxamidoadenosine (NECA) did not modify dopamine D2 receptor binding. In A2A-D2 cells CGS 21680 failed to induce or induced only a small increase in **adenosine** 3',5'-cyclic-monophosphate (cAMP) accumulation. In D2 cells NECA- or forskolin-induced adenylyl cyclase activation was not associated with any change in dopamine D2 receptor binding. These results indicate that adenylyl cyclase activation is not involved in the **adenosine** A2A receptor-mediated modulation of the binding characteristics of the dopamine D2 (long-form) receptor.

2/3,AB/60 (Item 60 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09143433 97081502 PMID: 8922745
Differential development of **adenosine** A1 and **A2b** receptors in the rat duodenum.
Peachey JA; Hourani SM; Kitchen I
Receptors and Cellular Regulation Research Group, School of Biological Sciences, University of Surrey, Guildford.
British journal of pharmacology (ENGLAND) Nov 1996, 119 (5) p949-58, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The development of the **adenosine** A1 and **A2b** receptors inducing relaxation of the rat duodenum was studied by use of a combination of functional and radioligand binding assays on rats aged between 5 and 30 days and compared with results previously found in adult rat duodenum. 2. 1,3-[3H]-dipropyl-8-cyclopentylxanthine ([3H]-DPCPX) bound with high affinity to a single site in duodenum preparations from rats aged 20, 25 and 30 days. At 10 and 15 days there was no detectable specific binding of [3H]-DPCPX. 3. The affinity (KD) of the binding site for [3H]-DPCPX was similar in membrane preparations from 20, 25 and 30 day old animals (1.58-1.2 nM), but the density (Bmax) of binding sites was found to increase up to 25 days where peak levels (72.0 +/- 9.5 fmol mg-1 protein) were observed and then decline at 30 days (45.5 +/- 2.9 fmol mg-1 protein) to levels commensurate with those previously determined in the adult rat duodenum. 4. In duodenum from 10 day old rats no responses to N6-cyclopentyladenosine (CPA, 1 nM-10 microM) were observed, at 15 days the duodenum responded to the highest concentration of CPA (3 microM) only, and at 20-30 days concentration-related responses were observed, with the potency of CPA increasing with an increase in age. DPCPX (10 nM) abolished the responses to CPA except at the highest concentration of CPA (3 microM) where the response was markedly attenuated, suggesting the presence of an A1, receptor. 5. In rat duodenum from animals of all ages (5-30 days), concentration-related responses to 5'-N-ethylcarboxamidoadenosine (NECA) were observed. The potency of NECA remained constant with an increase in age, whereas the maximum relaxation response increased from 20% at 5 days to 11[illegible] at 25 and 30 days. In the presence of 1 microM DPCPX a right-ward shift in the concentration-response curve to NECA was observed at all ages. In the presence of 10 nM DPCPX, the response to NECA was unaffected in the duodenum from animals aged 10 and 15 days. However, in duodenum from animals aged 20-30 days the concentration-response curve to NECA was shifted to the right suggesting that there is an A1 component to the action of NECA at these ages. Schild analysis of the effects of increasing concentrations of DPCPX versus NECA on the duodenum from 25 day old animals generated a slope of 0.62 suggesting that NECA acts at A1 and **A2b** receptors as in the adult. 6. The **A2b** -selective analogue, 2-[p-(carboxyethyl)-phenylethylamino]-5'-N-ethylcarboxamidoadenosine (CGS 21680) (10 nM-10 microM) was without effect on the carbachol-contracted duodenum from 15 day old rats and the duodenum from 25 day old rats responded to the highest concentration of CGS 21680 only, suggesting that the A2 receptors here, as in the adult, are not of the A2a subtype. The **adenosine antagonist**, 8-phenyltheophylline (8-PT) (10 microM), abolished the inhibitory effects of NECA (100 nM-100 microM) on 10, 15 and 25 day old rat duodenum indicating that the responses to NECA were not mediated via an **adenosine** A3 receptor. 7. These results show that **adenosine** A1 receptors in rat duodenum are present and functionally viable from day 20 onwards and that the density of A1 receptors varies with age, increasing up to day 25 and then declining at day 30 to a density commensurate with that found in the adult. The responses to CPA, mediated via the A1 receptor, increase with age in a similar fashion. In contrast however, the response to NECA was evident from day 5, the earliest age

studied, and from days 5-15 NECA acted via the **A2b** receptor subtype. However, from day 20 onwards NECA acted at a mixed population of A1 and **A2b** receptors. These results demonstrate the differential development of the A1 and the **A2b** receptors in the rat duodenum.

2/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09126770 97032159 PMID: 8878055
Adenosine A2A receptors mediate the inhibitory effect of **adenosine** on formyl-Met-Leu-Phe-stimulated respiratory burst in neutrophil leucocytes.
Fredholm BB; Zhang Y; van der Ploeg I
Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Naunyn-Schmiedeberg's archives of pharmacology (GERMANY) Aug-Sep 1996, 354 (3) p262-7, ISSN 0028-1298 Journal Code: NTQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Using the reverse transcription polymerase chain reaction (RT-PCR) we found that human neutrophils express mRNA for both A2A and **A2B** **adenosine** receptors, and using selective **adenosine** receptor agonists and antagonists we have characterized the type of **adenosine** receptor mediating inhibition of formyl-Met-Leu-Phe (fMLP)-induced oxidative burst. The order of potency of agonists was 5'-N-ethyl-carboxamidoadenosine (NECA) > 2-phenylaminoadenosine > 2-[p-(2-carbonyl-ethyl)-phenyl-ethylamino]-5'-N-ethyl-carboxamido **adenosine** (CGS 21680) > **adenosine** > N6-cyclopentyl-**adenosine**. This agrees with the agonist potency at human A2A receptors. The effect of **adenosine** was antagonized by 30 microM theophylline > caffeine = paraxanthine, i.e. concentrations close to those occurring in plasma after consumption of caffeine-containing beverages. The effect of NECA was unaltered by the A1 receptor **antagonist** 1,3-dipropyl-8-cyclopentylxanthine, but inhibited by the A2A receptor selective antagonists 4-amino-8-chloro-1-phenyl-[1,2,4]-triazolo[4,3-a]quinoxaline (CP 66,713), 1,3-dipropyl-8-(3,4-dimethoxystyryl) -7-methylxanthine (KF 17387) and 8-(3-chlorostyryl)caffeine as well as by the non-selective, non-xanthine **antagonist** 5-amino-9-chloro-2-(2-furyl)-[1,2,4]-triazolo-[1,5-c]quinazoline methane sulphonate (CGS 15943). The **adenosine** receptor mediated responses were antagonized by the protein kinase A blocker Rp-cyclic **adenosine** 3',5'-phosphorothioate (Rp-cAMP). In conclusion, the **adenosine**-induced inhibition of neutrophil activation is mediated by **adenosine** A2A receptors.

2/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09116375 96301591 PMID: 8732272
KW-3902, a selective high affinity **antagonist** for **adenosine** A1 receptors.
Nonaka H; Ichimura M; Takeda M; Kanda T; Shimada J; Suzuki F; Kase H
Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Shizuoka, Japan.
British journal of pharmacology (ENGLAND) Apr 1996, 117 (8) p1645-52, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. We demonstrate that 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902) is a very potent and selective **adenosine** A1 receptor **antagonist**, assessed by radioligand binding and cyclic AMP response in cells. 2. In rat forebrain **adenosine** A1 receptors labelled with

[3H]-cyclohexyladenosine (CHA), KW-3902 had a Ki value of 0.19 nM, whereas it showed a Ki value of [redacted]0 nM in rat striatal A2A receptors labelled with [3H]-2-[p-(2-carboxyethyl)-phenethylamino]-5'-N-ethylcarboxamidoadenosine (CGS21680), indicating 890 fold A1 receptor selectivity versus the A2A receptor. KW-3902 at 10 microM showed no effect on recombinant rat A3 receptors expressed on CHO cells. 3. Saturation studies with [3H]-KW-3902 revealed that it bound with high affinity (Kd = 77 pM) and limited capacity (Bmax = 470 fmol mg-1 of protein) to a single class of recognition sites. A high positive correlation was observed between the pharmacological profile of **adenosine** ligands inhibiting the binding of [3H]-KW-3902 and that of [3H]-CHA. 4. KW-3902 showed potent A1 antagonism against the inhibition of forskolin-induced cyclic AMP accumulation in DDT1 MF-2 cells by the A1-selective agonist, cyclopentyladenosine with a dissociation constant (KB value) of 0.34 nM. KW-3902 antagonized 5'-N-ethylcarboxamidoadenosine-elicited cyclic AMP accumulation via **A2B** receptors with a KB value of 52 nM. 5. KW-3902 exhibited marked species-dependent differences in the binding affinities. The highest affinity was for the rat A1 receptor (ki = 1.19 nM) and these values for guinea-pig and dog A1 receptors were 1.3 and 11 nM, respectively.

2/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09108813 96428977 PMID: 8832079
Activation of multiple sites by **adenosine** analogues in the rat isolated aorta.
Prentice DJ; Hourani SM
School of Biological Sciences, University of Surrey, Guildford.
British journal of pharmacology (ENGLAND) Jul 1996, 118 (6) p1509-17
, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The presence of A2 receptors mediating relaxation in the rat isolated aorta has been previously demonstrated. However, agonist dependency of the degree of rightward shift elicited by 8-sulphophenyltheophylline (8-SPT) led to the suggestion that the population of receptors in this tissue is not a homogeneous one. In this study we have re-examined the effects of 8-SPT in the absence and presence of the NO synthase inhibitor L-NAME (NG-nitro-L-arginine methyl ester) and investigated antagonism of responses by the potent A2a receptor ligands PD 115,199 (N-[2-dimethylamino)ethyl]-N-methyl-4-(2,3,6,7-tetrahydro-2,6-dioxo-1,3 dipropyl-1H-purin-8-yl)) benzene sulphonamidexanthine), ZM 241385 (4-(2-[7-amino-2-(2-furyl) [1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl amino]ethyl phenol), and CGS 21680 (2-[p-(2-carboxyethyl)phenylamino]-5'-N-ethyl carboxamidoadenosine). We have also investigated the **antagonist** effects of BWA1433 (1,3-dipropyl-8-(4-acrylate)phenylxanthine) which has been shown to have affinity at rat A3 receptors. 2. **Adenosine**, R-PIA (N6-R-phenylisopropyl **adenosine**), CPA (N6-cyclopentyladenosine) and NECA (5'-N-ethylcarboxamidoadenosine) all elicited relaxant responses in the phenylephrine pre-contracted rat isolated aorta with the following potency order (p[A50] values in parentheses): NECA (7.07 +/- 0.11) > R-PIA (5.65 +/- 0.10) > CPA (5.05 +/- 0.12) > **adenosine** (4.44 +/- 0.12). 3. 8-SPT (10-100 microM) caused parallel rightward shifts of the E/[A] curves to NECA (pKB = 5.23 +/- 0.16). A smaller rightward shift of E/[A] curves to CPA was observed (pA2 = 4.85 +/- 0.17). However, no significant shifts of E/[A] curves to either **adenosine** or R-PIA were observed. 4. In the absence of endothelium E/[A] curves to NECA and CPA were right-shifted compared to controls. However, removal of the endothelium did not produce a substantial shift of **adenosine** E/[A] curves, and E/[A] curves to R-PIA were unaffected by removal of the endothelium. 5. In the presence of L-NAME (100 microM) E/[A] curves to NECA and CPA were right-shifted. However, no further shift of the CPA E/[A] curve was obtained when 8-SPT (50 microM) was administered concomitantly. The locations of curves to

R-PIA and **adenosine** were unaffected by L-NAME (100 microM). 6. In the presence of PD 115,199 (0.1 microM) a parallel rightward shift of NECA E/[A] curves was observed (pA2 = 7.50 +/- 0.19). PD 115,199 (0.1 and 1 microM) gave smaller rightward shifts of E/[A] curves to R-PIA and CPA, but E/[A] curves to **adenosine** were not significantly shifted in the presence of PD 115,199 (0.1 or 1 microM). 7. The presence of ZM 241385 (3 nM-0.3 microM) caused parallel rightwad shifts of NECA E/[A] curves (pKB = 9.73 +/- 0.11). No significant shifts of E/[A] curves to **adenosine**, CPA or R-PIA were observed in the presence of 0.1 microM ZM 241385. 8. CGS 21680 (1 microM) elicited a relaxant response equivalent to approximately 40% of the NECA maximum response. In the presence of this concentration of CGS 21680, E/[A] curves to NECA were right-shifted in excess of 2-log units, whereas E/[A] curves to R-PIA were not significantly shifted. 9. BWA1433 (100 microM) caused a small but significant right-shift of the E/[A] curve to R-PIA yielding a pA2 estimate of 4.1 IB-MECA (N6-(3-iodo-benzyl)**adenosine** -5(1)-N-methyl uronamide) elicited relaxant responses which were resistant to blockade by 8-SPT (p[A]50 = 5.26 +/- 0.13). 10. The results suggest that whereas relaxations to NECA (10 nM-1 microM) are mediated via **adenosine** A2a receptors, which are located at least in part on the endothelium, R-PIA and CPA may activate **A2b** receptors on the endothelium and an additional, as yet undefined site, which is likely to be located on the smooth muscle and which is not susceptible to blockade by 8-SPT, PD 115,199 or ZM 241385. This site is unlikely to be an A3 receptor since the very small shift obtained in the presence of BWA1433 (100 microM), and the low potency of IB-MECA is not consistent with the affin

2/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09000149 96422742 PMID: 8825359
Characterization of P1-purinoceptors on rat isolated duodenum longitudinal muscle and muscularis mucosae.
Nicholls J; Brownhill VR; Hourani SM
Receptors and Cellular Regulation Research Group, University of Surrey, Guildford.
British journal of pharmacology (ENGLAND) Jan 1996, 117 (1) p170-4, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. P1-purinoceptors mediating relaxation of the rat duodenum longitudinal muscle and contraction of the rat duodenum muscularis mucosae were characterised by the use of **adenosine** and its analogues, 5'-N-ethylcarboxamidoadenosine (NECA), N6-cyclopentyl-**adenosine** (CPA), N6-(phenylisopropyl)**adenosine** (R-PIA), 2-chloroadenosine (2-CADO) and 2-p-((carboxyethyl)phenethylamino)-5'-carboxamidoadenosine (CGS21680), as well as the P1-purinoceptor **antagonist** 8-phenyltheophylline (8-PT) and the A1-selective **antagonist**, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX). 2. In the rat duodenum longitudinal muscle, the order of potency of the **adenosine** agonists was CPA > NECA > **adenosine** > CGS21680. DPCPX antagonized responses to CPA and NECA at a concentration of 1 nM suggesting that they are acting at A1 receptors. A Schild plot versus CPA gave a slope near to unity (slope = 0.955) and a pA2 of 9.8 confirming that CPA was acting via A1 receptors. Schild analysis for DPCPX versus NECA, however, gave a slope of 0.674 suggesting that NECA was acting on both A1 and A2 receptors. CGS21680, a selective A2a agonist, was much less potent than **adenosine** suggesting that the A2 receptors are of the **A2b** subtype. 3. In the rat duodenum muscularis mucosae, the order of potency of the **adenosine** agonists was NECA > or = R-PIA = CPA > 2-CADO > **adenosine**, and DPCPX antagonized responses to CPA and NECA at a concentration of 1 microM. CGS21680, at a concentration of 10 microM, had no effect on this tissue. This suggests the presence of A2 receptors in this tissue and that they are

of the **A2b** subtype. 4. These results are in agreement with previous studies in the whole [redacted]odenum showing the presence [redacted]1 and **A2b** receptors causing relaxation, and this shows that the longitudinal muscle dominates the response of the whole tissue. In addition, a contractile **A2b** receptor has been revealed on the muscularis mucosae, the first time this subtype has been reported to elicit an excitatory response in a smooth muscle preparation.

2/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08899200 96110991 PMID: 8848003
G protein-dependent activation of phospholipase C by **adenosine** A3 receptors in rat brain.
Abbracchio MP; Brambilla R; Ceruti S; Kim HO; von Lubitz DK; Jacobson KA; Cattabeni F
Institute of Pharmacological Sciences, University of Milan, School of Pharmacy, Italy.
Molecular pharmacology (UNITED STATES) Dec 1995, 48 (6) p1038-45, ISSN 0026-895X Journal Code: NGR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The recently cloned G protein-coupled **adenosine** A3 receptor has been proposed to play a role in the pathophysiology of cerebral ischemia. Because phospholipase C activation occurs as a very early response to brain ischemia, we evaluated the ability of A3- selective and nonselective **adenosine** analogues to elicit phosphoinositide hydrolysis. In myo-[3H]inositol-labeled rat striatal and hippocampal slices, A3 agonists stimulated formation of [3H]inositol phosphates in a concentration-dependent manner. In striatum, the potency order was 2-chloro-N6-(3-iodobenzyl)- **adenosine**-5'-N-methyluronamide > or = N6-(3-iodobenzyl)- **adenosine**-5'-N-methyluronamide >> N-methyl-1,3-di-n-butylxanthine-7-beta-D-ribofuronamide > or = 5'-N-ethylcarboxamidoadenosine > or = N6-2-(4-aminophenyl)-ethyladenosine > N6-(p-sulfophenyl)-**adenosine** = 1,3-dibutylxanthine-7- riboside, which is identical to the potency order in binding studies at cloned rat A3 receptors. Stimulation of phospholipase C activity was abolished by guanosine-5'-O-(2-thiodiphosphate), confirming the involvement of a G protein-coupled receptor. Activation of phospholipase C was higher in the striatum than in the hippocampus, consistent with A3 receptor densities. Stimulation of phospholipase C activity by **adenosine** analogues was only modestly antagonized by xanthine derivatives and at much higher concentrations than needed for blocking **adenosine** A1, A2A, and **A2b** receptors. In the presence of an A1/A2 **antagonist**, a selective A3 in rat striation. Thus, stimulation of phospholipase C activity agonist only weakly inhibited forskolin-stimulated adenylyl cyclase activity represents a principal transduction mechanism for A3 receptors in mammalian brain, and perhaps A3 receptor-mediated increases of inositol phosphates in the ischemic brain contribute to neurodegeneration by raising intracellular calcium levels.

2/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08898055 95330334 PMID: 7606456
Hyperexcitability in CA1 of the rat hippocampal slice following hypoxia or **adenosine**.
Doolette DJ; Kerr DI
Department of Anaesthesia and Intensive Care, University of Adelaide, Australia.
Brain research (NETHERLANDS) Apr 17 1995, 677 (1) p127-37, ISSN 0006-8993 Journal Code: B5L

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Participation of **adenosine** receptors in the depression of synaptic transmission during hypoxia, and the production of multiple populations spikes in the pyramidal neurons following hypoxia, has been investigated in the CA1 area of the rat hippocampal slice. A method is presented for analysing such hyperexcitability, using input/output curves of the second population spike. This method provides evidence that rebound hyperexcitability following hypoxia or prolonged **adenosine**-mediated inhibition results from an increase in excitability of the CA1 pyramidal neurons rather than from an increase in excitatory neurotransmitter release. Hypoxia-induced depression of the synaptic components of evoked field potentials was blocked in a concentration dependent manner by the selective A1 receptor **antagonist** 8-cyclopentyltheophylline (8-CPT), demonstrating extracellular accumulation of **adenosine** during hypoxia. Upon reoxygenation of slices following 30 min hypoxia, multiple population spikes were evoked by a single orthodromic stimulus in slices that exhibited only a single population spike prior to hypoxia. Such post-hypoxic hyperexcitability was not prevented by superfusion of slices with 8-CPT during hypoxia. Depression of synaptic transmission by 30 min superfusion of slices with 50 microM **adenosine** was also followed, upon washout, by the appearance of multiple population spikes. However, such hyperexcitability could not be produced by superfusion with **adenosine** analogues selective for A1 receptors, cyclopentyladenosine, selective for A2a receptors, 2-p-(2-carboxyethyl)phenetheylamino-5'-ethylcarboxamidoadenosine (CGS 21680), or active at A2a and **A2b** receptors, N6-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]**adenosine**, suggesting that **adenosine** receptors other than the A1, A2a or **A2b** subtypes are involved in its generation.

2/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08870031 96223450 PMID: 8632302

The non-xanthine heterocyclic compound SCH 58261 is a new potent and selective A2a **adenosine** receptor **antagonist**.

Zocchi C; Ongini E; Conti A; Monopoli A; Negretti A; Baraldi PG; Dionisotti S

Shering-Plough Research Institute, Milan, Italy.

Journal of pharmacology and experimental therapeutics (UNITED STATES) Feb 1996, 276 (2) p398-404, ISSN 0022-3565 Journal Code: JP3

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We have characterized the in vitro pharmacological profile of the new potent and selective A2a **adenosine** receptor **antagonist** SCH 58261 [7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine]. In binding studies on rat and bovine brain tissues, SCH 58261 showed affinity in the low nanomolar range at A2a **adenosine** striatal receptors and good A2a **adenosine** vs. A1 **adenosine** selectivity (about 50- to 100-fold in rat and bovine brain, respectively). SCH 58261 did not show affinity for either the A3 **adenosine** receptor or other receptors at concentrations up to 1 microM. Saturation experiments on rat A1 and A2a **adenosine** receptors indicated the competitive nature of the antagonism. SCH 58261 antagonized competitively the effects induced by the A2a **adenosine** -selective agonist CGS 21680 (2-[4-(2-carboxyethyl)-phenethyl-amino]-5'-N- ethylcarboxamidoadenosine) in two functional assays, such as inhibition of rabbit platelet aggregation and porcine coronary artery relaxation. Specifically, the compound showed pA2 values of 7.9 and 9.5, respectively. SCH 58261 (300 nM) failed to antagonize 5'-N-ethylcarboxamidoadenosine-induced vasorelaxation in the isolated guinea pig aorta, a response mediated by **A2b adenosine** receptors. Likewise, at the same concentration, the compound weakly

inhibited the A1 **adenosine** -mediated negative chronotropic effect induced by 2-chloro-N6-cyclopentyladenosine in the [redacted]ated rat atria. These data show that SCH 58261 is a potent and selective non-xanthine A2a **adenosine antagonist** which has competitive properties in biological responses mediated by this receptor subtype. The compound is of interest for investigating the biological role of A2a **adenosine** receptors and deserves further attention to clarify the therapeutic potential of A2a antagonists.

2/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08869402 96192129 PMID: 8627294
Adenosine A2b receptors mediate an increase in interleukin (IL)-6 mRNA and IL-6 protein synthesis in human astroglioma cells.
Fiebich BL; Biber K; Gyufko K; Berger M; Bauer J; van Calker D
Psychiatrische Klinik, Universitat Freiburg, Germany.
Journal of neurochemistry (UNITED STATES) Apr 1996, 66 (4) p1426-31, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The cytokine interleukin (IL)-6 has recently been demonstrated to play a role in the pathology of Alzheimer's disease (AD). The mechanisms leading to increased IL-6 levels in brains of AD patients are still unknown. Because in experimental animals ischemia increases both the levels of cytokines and the extracellular concentrations of **adenosine** in the brain, we hypothesized that these two phenomena may be functionally connected and that **adenosine** might increase IL-6 gene expression in the brain. Here we show that the mixed A1 and A2 agonist 5'-(N-ethylcarboxamido) **adenosine** (NECA) induces an increase in IL-6 mRNA levels and protein synthesis in the human astrocytoma cell line U373 MG. The A1-specific agonists R-phenylisopropyladenosine and cyclopentyladenosine are much less potent, and the A2a-specific agonist CGS-21680 shows only marginal effects. Increased levels of mRNA are already found within 30 min after NECA treatment. The A2a-selective antagonists 8-(3-chlorostyryl) caffeine and KF17837 [(E)-8-(3,4-dimethoxystyryl)-1,3-di propyl-7-methylxanthine] , which have also some antagonistic properties at **A2b** receptors, and the nonspecific **adenosine antagonist** 8-phenyltheophylline were equipotent at inhibiting the NECA-induced increase in IL-6 protein synthesis, whereas the specific A1 **antagonist** 8-cyclopentyl-1,3 dipropylxanthine is much less potent. The results indicate that **adenosine A2b** receptors participate in the regulation of the IL-6 gene in astrocytoma cells.

2/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08850805 96223462 PMID: 8632314
Characterization of 8-(N-methylisopropyl)amino-N6-(5'-endohydroxy-endonorbornyl)-9-methyladenine (WRC-0571), a highly potent and selective, non-xanthine **antagonist** of A1 **adenosine** receptors.
Martin PL; Wysocki RJ; Barrett RJ; May JM; Linden J
Department of Pharmacology, Discovery Therapeutics Inc., Richmond, Virginia, USA.
Journal of pharmacology and experimental therapeutics (UNITED STATES) Feb 1996, 276 (2) p490-9, ISSN 0022-3565 Journal Code: JP3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Previous studies in our laboratory identified N6-endonorbornyl-9-methylad enine (N-0861) as a highly selective (100-fold) A1-**adenosine** receptor **antagonist** (KB = 500 nM). However, its moderate potency limits the

degree of A1-receptor blockade that can be achieved by systemically administered N-0861. Structure activity studies were undertaken to invent a compound that had greater affinity for the A1-**adenosine** receptors than N-0861. C8-N-methylisopropylamino-N6-5'-endohydroxy-N-0861 (WRC-0571) inhibited [3H]-N6-cyclohexyladenosine (CHA) binding to guinea pig A1-receptors with a Ki value of 1.1 nM. WRC-0571 was 200-fold less potent at inhibiting [3H]-5'-N-ethylcarboxamidoadenosine binding to bovine A2a receptors (Ki = 234 nM). WRC-0571 also inhibited the binding of radioligands to cloned human A1, A2a and A3 **adenosine** receptors with affinities of 1.7, 105 and 7940 nM, respectively. Thus in human **adenosine** receptors, WRC-0571 is 62-fold selective for the A1 vs. A2a and 4670-fold selective for the A1 vs. A3 receptors; WRC-0571 is therefore the most A1 vs. A3 selective compound yet described. In guinea pig isolated atria, WRC-0571 antagonized the A1-mediated negative inotropic responses to 5'-N-ethylcarboxamidoadenosine (NECA) with a KB of 3.4 nM. WRC-0571 was more than 2500-fold less potent at antagonizing NECA-induced **A2b** -mediated relaxation in guinea pig aorta. In anesthetized rats WRC-0571 antagonized **adenosine**-induced bradycardia at concentrations as low as 1 nmol/kg but failed to antagonize A2-mediated hindquarter vasodilation at concentrations up to 10,000 nmol/kg. WRC-0571 is orally active at concentrations as low as 0.3 mumol/kg. WRC-0571 is therefore a highly potent, highly selective **antagonist** of A1-**adenosine** receptors both in vitro and in vivo.

2/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08839463 96189020 PMID: 8613241
Adenosine inhibits growth of rat aortic smooth muscle cells. Possible role of **A2b** receptor.
Dubey RK; Gillespie DG; Osaka K; Suzuki F; Jackson EK
Center for Clinical Pharmacology, Department of Medicine, University of Pittsburgh Medical Center, PA 15213-2582, USA.
Hypertension (UNITED STATES) Mar 1996, 27 (3 Pt 2) p786-93, ISSN 0194-911X Journal Code: GK7
Contract/Grant No.: HL35909, HL, NHLBI; HL40319, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Abnormal growth of vascular smooth muscle cells (SMC) is frequently associated with hypertension and atherosclerosis, and homeostasis within a normal vessel is maintained by the balanced generation of both vasoconstrictors and vasodilators. Moreover, several endogenous vasoconstricting factors induce SMC growth, whereas several vasodilators inhibit SMC growth. Inasmuch as **adenosine** is a potent vasodilator, it is possible that it too could inhibit SMC growth. Hence, the effects of **adenosine** (10(-8) to 10(-3) mol/L), 2-chloroadenosine (a stable analogue of **adenosine** ; 10(-8) to 10(-3) mol/L), and 8-bromo-cAMP (10(-8) to 10(-3) mol/L) on fetal calf serum (FCS; 2.5%)-induced growth of rat aortic SMC were evaluated. Growth was analyzed by assaying DNA synthesis (thymidine incorporation in SMC pulsed for 4 hours with 1 microCi/mL [3H]thymidine) and cell proliferation (change in cell number). Growth-arrested SMC were treated with 2.5% FCS in the presence and absence of **adenosine**, 2-chloroadenosine, or 8-bromo-cAMP for 24 hours for DNA synthesis or 4 days for cell proliferation. All three substances inhibited DNA synthesis and cell proliferation in a concentration-dependent manner. Compared with **adenosine** , 2-chloroadenosine was more potent in inhibiting growth. The inhibitory effects of 2-chloroadenosine were reversed by KF17837 (a specific A2 receptor **antagonist**) but not by DPCPX (a specific A1 receptor **antagonist**). Furthermore, the inhibitory effects of 2-chloroadenosine were not mimicked by CGS21680 (an A2a receptor agonist), and the effects of N6-cyclopentyladenosine (CPA; an A1 receptor agonist) were not markedly more potent than those of 2-chloroadenosine, suggesting that the inhibitory effects of

adenosine are possibly mediated via **A2b** receptors. These studies provide evidence that **adenosine** inhibits SMC growth and suggest that a decrease in local levels of **adenosine** may initiate SMC growth and contribute to the vascular remodeling process observed in hypertension and atherosclerosis.

2/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08777410 96013661 PMID: 7560091
Adenosine A2b receptors evoke interleukin-8 secretion in human mast cells. An enprofylline-sensitive mechanism with implications for asthma.
Feoktistov I; Biaggioni I
Department of Medicine, Vanderbilt University, Nashville, Tennessee 37232-2195, USA.
Journal of clinical investigation (UNITED STATES) Oct 1995, 96 (4) p1979-86, ISSN 0021-9738 Journal Code: HS7
Contract/Grant No.: HL-14192, HL, NHLBI; RR00095, RR, NCRR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine potentiates mast cell activation, but the receptor type and molecular mechanisms involved have not been defined. We, therefore, investigated the effects of **adenosine** on the human mast cell line HMC-1. Both the A2a selective agonist CGS21680 and the A2a/**A2b** nonselective agonist 5'-N-ethylcarboxamidoadenosine (NECA) increased cAMP, but NECA was fourfold more efficacious and had a Hill coefficient of 0.55, suggesting the presence of both A2a and **A2b** receptors. NECA 10 microM evoked IL-8 release from HMC-1, but CGS21680 10 microM had no effect. In separate studies we found that enprofylline, an antiasthmatic previously thought to lack **adenosine** antagonistic properties, is as effective as theophylline as an **antagonist** of **A2b** receptors at concentrations achieved clinically. Both theophylline and enprofylline 300 micro completely blocked the release of IL-8 by NECA. NECA, but not CGS21680, increases inositol phosphate formation and intracellular calcium mobilization through a cholera and pertussis toxin-insensitive mechanism. In conclusion, both A2a and **A2b** receptors are present in HMC-1 cells and are coupled to adenylate cyclase. In addition, **A2b** receptors are coupled to phospholipase C and evoke IL-8 release. This effect is blocked by theophylline and enprofylline, raising the possibility that this mechanism contributes to their antiasthmatic effects.

2/3,AB/72 (Item 72 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08774460 95366861 PMID: 7639616
Characterization of the **adenosine** receptors in the airways.
Pauwels RA; Joos GF
Department of Respiratory Diseases, University Hospital Ghent, Belgium.
Archives internationales de pharmacodynamie et de therapie (BELGIUM) Jan-Feb 1995, 329 (1) p151-60, ISSN 0003-9780 Journal Code: 7EK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine causes bronchoconstriction both in vivo and in vitro in human asthmatics. In an in vivo rat model of **adenosine**-induced bronchoconstriction, the order of bronchoconstrictor potency of **adenosine** analogues was NECA = CPA > APNEA > CHA > R-PIA > CGS21680. This order of potency does not fit with the classical order of potency for a single subtype of **adenosine** receptors. The complete lack of bronchoconstrictory activity of CGS21680 suggests, nevertheless, that the A2A receptor subtype is not involved in the **adenosine**-induced

bronchoconstriction. A remarkable finding was the dose-response curve to APNEA, which is thought to have some selective activity on the A3 receptor. The A2A-selective **antagonist** KF17837 (10(-7) to 10(-5) mol/kg) had no significant inhibitory activity on the **adenosine** -induced bronchoconstriction. The A1 antagonists, KF15372 and KW3902, both significantly inhibited the NECA-induced bronchoconstriction in BDE rats. We, therefore, conclude that the **adenosine** -induced bronchoconstriction in the rat is most likely due to binding of **adenosine** to different receptor subtypes including the A1, **A2B** and A3 subtypes.

2/3,AB/73 (Item 73 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08774045 95359887 PMID: 7633334
Biochemical and pharmacological evidence for the presence of A1 but not A2a **adenosine** receptors in the brain of the low vertebrate teleost Carassius auratus (goldfish).
Rosati AM; Traversa U; Lucchi R; Poli A
Institute of Pharmacology and Pharmacognosy, Faculty of Pharmacy, University of Trieste, Italy.
Neurochemistry international (ENGLAND) Apr 1995, 26 (4) p411-23, ISSN 0197-0186 Journal Code: BNU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In whole brain membranes of goldfish, 3H-chlorocyclopentyladenosine bound to **adenosine** A1 receptors. The A1 receptors were ubiquitously distributed in the brain with a maximum in the hypothalamus and a minimum in the spinal cord. In superfused goldfish cerebellar slices, cyclohexyladenosine inhibited the cyclic AMP accumulation stimulated by forskolin and the selective **adenosine** A1 receptor **antagonist**, 8-cyclopentyltheophylline, reversed this effect. In the same brain preparation, 30 mM K+ stimulated the release of glutamate, glutamine, glycine and GABA in a Ca(2+)-dependent manner, whereas the aspartate and taurine release was Ca(2+)-independent. Cyclohexyladenosine, in a dose-dependent manner, inhibited the 30 mM K(+)-evoked release of glutamate whereas that of aspartate was unaffected. The CHA inhibition of glutamate-evoked release was reversed by 8-cyclopentyltheophylline. The **adenosine** A2a receptors were not detectable in whole brain membranes of goldfish either using the specific agonist 3H-CGS 21680 or 3H-5'-N-ethylcarboxamidoadenosine. The presence of **A2b** seems to be suggested by the NECA stimulation of cyclic AMP accumulation, which was reversed by 8-cyclopentyltheophylline. The results, taken together, indicate that **adenosine** has a neuromodulatory function in the nervous system of lower vertebrates which is comparable to that described in mammalian brain.

2/3,AB/74 (Item 74 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08769982 95289461 PMID: 7771537
Adenosine -induced vasodilation: receptor characterization in pulmonary circulation.
Haynes J; Obiako B; Thompson WJ; Downey J
Department of Medicine, University of South Alabama College of Medicine, Mobile 36688.
American journal of physiology (UNITED STATES) May 1995, 268 (5 Pt 2) pH1842-8, ISSN 0002-9513 Journal Code: 3U8
Contract/Grant No.: HL-02352, HL, NHLBI; HL-46494, HL, NHLBI; P60-HL-38639, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article

Record type: Completed

Adenosine mediates [redacted]cular smooth muscle relaxat[redacted] in the pulmonary circulation. The A2 receptor has been suggested to mediate **adenosine**-induced vasodilation (AIV). In this study, the effect(s) of selective **adenosine** agonist and **antagonist** on the hypoxic pressor response (HPR) was assessed in the isolated blood-perfused rat lung. **Adenosine** (0.075-7.5 mM) infusion (0.125 ml/min) into the pulmonary artery dose dependently attenuated the HPR. AIV was mimicked by 10 microM 5'-(N-ethylcarboxamido)**adenosine** (NECA), a nonselective **adenosine** agonist. **Adenosine** - and NECA-induced vasodilation were attenuated by 67 microM 8-(p-sulfophenyl)theophylline. In contrast, NECA-induced vasodilation was not attenuated by the A1 **antagonist** 8-cyclopentyl-1,3-dipropylxanthine (1 microM). At 10 microM, a minimal vasodilatory effect was seen with the nonselective **adenosine** agonists CV-1808 and N6-(2-phenylisopropyl)**adenosine** (R-PIA) compared with NECA. The highly selective A2a agonist 2-[p-(2-carboxyethyl)phenyl amino]-5'-N-ethyl carboxamido **adenosine** (CGS-21680C, 10 microM) and A1 agonist 2-chloro-N6-cyclopentyladenosine (CCPA, 10 microM) had no vasodilatory effect. Neither the K+ channel blockers tetraethylammonium chloride (10 mM) and glibenclamide (100 microM) nor the NO synthase inhibitor N omega-nitro-L-arginine methyl ester attenuated NECA-induced vasodilation. These findings suggest that AIV is mediated via the **A2b** receptor and that AIV occurs via an NO-independent mechanism.

2/3,AB/75 (Item 75 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08766864 95127489 PMID: 7712011

Functional characterization of the **adenosine** receptor mediating inhibition of intestinal secretion.

Hancock DL; Coupar IM

School of Pharmacology, Unit of Addictive Drug Research, Victorian College of Pharmacy, Monash University, Parkville, Australia.

British journal of pharmacology (ENGLAND) Jan 1995, 114 (1) p152-6, ISSN 0007-1188 Journal Code: B00

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

1. Previous studies have shown that the mixed A1/A2 **adenosine** agonist 5'-N-ethylcarboxamido-**adenosine** (NECA) inhibits intestinal fluid secretion which is thought to contribute to its antidiarrhoeal effect in the rat. The aim of this study was to characterize the **adenosine** receptor mediating this antisecretory effect via functional studies using a range of selective agonists and antagonists and by applying the pharmacological criteria of relative agonist and **antagonist** potencies. 2. **Adenosine** agonists and antagonists were administered i.v. to anaesthetized rats. Intestinal secretion was then stimulated by i.a. infusion of vasoactive intestinal peptide (VIP, 0.8 microgram min-1) and the net fluid transport across the wall of the jejunum was measured by a recirculation technique. 3. The rank order of agonist potency to reduce the response to VIP was: NECA > N6-cyclopentyladenosine (CPA) > R-N6-(2-phenylisopropyladenosine) (R-PIA) > S-PIA > chloroadenosine (2-CADO) > 2-phenylaminoadenosine (CV-1808). This order best complies with the rank order of agonist potency that represents activation of the recently described **A2B** receptor: NECA > 2-CADO > R-PIA = CHA > S-PIA > = CV-1808 > = CGS-21680. The most potent agonists (NECA, CPA and RPIA) had ED50 values in the low microgram range. 4. The anitsecretory action of NECA (submaximal dose of 40 micrograms kg-1) was antagonized equally (approximately 50%) by the selective **adenosine** antagonists 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 0.1 mg kg-1) and 8-phenyltheophylline (8-PT, 0.1 mg kg-1). This equipotent activity indicates the presence of an A2 and not an A1 receptor.(ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/76 (Item 76 [redacted] file: 155)
DIALOG(R)File 155:MEDLINE(R)

08764318 95138214 PMID: 7836474
The **A2b adenosine** receptor mediates cAMP responses to **adenosine** receptor agonists in human intestinal epithelia.
Strohmeier GR; Reppert SM; Lencer WI; Madara JL
Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02115.
Journal of biological chemistry (UNITED STATES) Feb 3 1995, 270 (5) p2387-94, ISSN 0021-9258 Journal Code: HIV
Contract Grant No.: DK-35932, DK, NIDDK; DK-42125, DK, NIDDK; DK-47662, DK, NIDDK; -
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine is thought to be a major effector in immunological stimulation of Cl- secretion in intestinal epithelia. Previous studies indicate that both apical and basolateral domains of intestinal epithelial cells possess functionally defined **adenosine** receptors. However, it is unclear whether the same receptor subclass is expressed, what the receptor subclass(es) is, or how the receptors signal the Cl- secretory response. We now characterize the intestinal epithelial **adenosine** receptor subtype using the model epithelium, T84. Both apical and basolateral **adenosine** receptor agonist response profiles revealed a hierarchy (ED50) of 5'-(N-ethylcarboxamido)**adenosine** > **adenosine** > CGS-21680. Similarly inhibition studies revealed identical ID50 hierarchies for apical and basolateral antagonism by xanthine amine congener > 1,3-diethyl-8-phenylxanthine > aminophylline. Analyses of both agonist and **antagonist** pharmacological hierarchies in Chinese hamster ovary cells stably expressing the **A2b** receptor revealed these same hierarchies. Northern blots performed on RNA extracted from polarized T84 monolayers demonstrated no detectable message for A1 or A2a **adenosine** receptor, but strong hybridization was detected for the **A2b adenosine** receptor. Subsequent Northern blots of RNA prepared from human alimentary tract revealed that **A2b adenosine** receptor message was heavily expressed throughout the colon, in the appendix, and more modestly expressed in the small intestine (ileum). Analyses of cAMP generation in T84 cells in response to **adenosine** indicated that the basolateral **A2b** receptor elicits Cl- secretion through this signaling pathway. Stimulation of Cl- secretion through the apical **A2b** receptor exhibited relatively small but significant increases in cAMP compared with basolateral stimulation. The protein kinase A inhibitor H-89, used at concentrations that did not affect short circuit current responses to the Ca(2+)-mediated agonist carbachol, effectively inhibited short circuit current elicited by either apical or basolateral **adenosine** . These data suggest that the major intestinal epithelial **adenosine** receptor is the **A2b** subclass, which is positively coupled to adenylate cyclase. Such observations have potentially important implications for the treatment of diarrheal diseases.

2/3,AB/77 (Item 77 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08760853 96110982 PMID: 8848012
125I-4-(2-[7-amino-2-[2-furyl][1,2,4]triazolo[2,3-a][1,3,5] triazin-5-yl-amino]ethyl)phenol, a high affinity **antagonist** radioligand selective for the A2a **adenosine** receptor.
Palmer TM; Poucher SM; Jacobson KA; Stiles GL
Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.
Molecular pharmacology (UNITED STATES) Dec 1995, 48 (6) p970-4, ISSN 0026-895X Journal Code: NGR

Contract/Grant No.: P50HL54314, HL, NHLBI; RO1HL35134, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The A2a **adenosine** receptor (AR) mediates several important physiological effects of **adenosine**, including vasodilation and inhibition of platelet aggregation. Until recently, no **antagonist** radioligand of sufficient selectivity or affinity was available. We describe the synthesis and characterization by radioligand binding of 125I-4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a]-[1,3,5]triazin-5-yl-amino]ethyl)phenol (125I-ZM241385) in membranes from two cell types that express A2a ARs. Membranes from Chinese hamster ovary (CHO) cells expressing a recombinant canine A2a AR bound 125I-ZM241385 with high affinity, and agonist competition experiments with 2-(p-carboxyethyl)-phenylamino-5'-N-carboxamidoadenosine, 5'-N-ethylcarboxamidoadenosine, and (-)-N6[(R)-phenylisopropyl]**adenosine** revealed a potency order characteristic of an A2a AR binding site. Membranes from bovine striatum, which contain a native A2a AR, also bound 125I-ZM214385 with similarly high affinity and also displayed a pharmacological profile for displacement of radioligand binding that was consistent with that of an A2a AR. Also, under conditions in which 125I-ZM241385 bound with high affinity to a recombinant rat A2a AR expressed in CHO cells, no specific binding was detectable in membranes from CHO cells expressing functional rat A1, **A2b**, or A3 ARs, indicating that over the range of concentrations used in radioligand binding assays, 125I-ZM214385 is a highly selective **antagonist** radioligand for study of A2a ARs within a given species.

2/3,AB/78 (Item 78 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08640836 96090479 PMID: 7582508

The in vitro pharmacology of ZM 241385, a potent, non-xanthine A2a selective **adenosine** receptor **antagonist**.

Poucher SM; Keddie JR; Singh P; Stoggall SM; Caulkett PW; Jones G; Coll MG

Cardiovascular and Metabolism Department, ZENECA Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire.

British journal of pharmacology (ENGLAND) Jul 1995, 115 (6) p1096-102. ISSN 0007-1188 Journal Code: B00

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

1. This paper describes the in vitro pharmacology of ZM 241385 (4-(2-[7-amino-2-(2-furyl)[1,2,4]-triazolo[2,3-a][1,3,5]triazin-5-yl amino]ethyl) phenol), a novel non-xanthine **adenosine** receptor **antagonist** with selectivity for the A2a receptor subtype. 2. ZM 241385 had high affinity for A2a receptors. In rat phaeochromocytoma cell membranes, ZM 241385 displaced binding of tritiated 5'-N-ethylcarboxamidoadenosine (NECA) with a pIC50 of 9.52, (95% confidence limits, c.l., 9.02-10.02). In guinea-pig isolated Langendorff hearts, ZM 241385 antagonized vasodilatation of the coronary bed produced by 2-chloroadenosine (2-CADO) and 2-[p-(2-carboxyethyl) phenethylamino]-5'-N-ethylcarboxamidoadenosine (CGS21680) with pA2 values of 8.57 (c.l., 8.45-8.68) and 9.02 (c.l., 8.79-9.24) respectively. 3. ZM 241385 had low potency at **A2b** receptors and antagonized the relaxant effects of **adenosine** in the guinea-pig aorta with a pA2 of 7.06, (c.l., 6.92-7.19). 4. ZM 241385 had a low affinity at A1 receptors. In rat cerebral cortex membranes it displaced tritiated R-phenylisopropyladenosine (R-PIA) with a pIC50 of 5.69 (c.l., 5.57-5.81). ZM 241385 antagonized the bradycardic action of 2-CADO in guinea-pig atria with a pA2 of 5.95 (c.l., 5.72-6.18). 5. ZM 241385 had low affinity for A3 receptors. At cloned rat A3 receptors expressed in chinese hamster ovary cells, it displaced iodinated aminobenzyl-5'-N-methylcarboxamido **adenosine** (AB-MECA) with a pIC50 of 3.82 (c.l., 3.67-4.06). 6. ZM 241385 had no significant

additional pharmacological effects on the isolated tissues used in these studies at concentrations three orders of magnitude greater than those which block A2a receptors.(ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/79 (Item 79 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08560533 95341510 PMID: 7616413
Adenosine A1 and **A2b** receptors coupled to distinct interactive signaling pathways in intestinal muscle cells.
Murthy KS; McHenry L; Grider JR; Makhlouf GM
Department of Medicine, Medical College of Virginia, Richmond, USA.
Journal of pharmacology and experimental therapeutics (UNITED STATES) Jul 1995, 274 (1) p300-6, ISSN 0022-3565 Journal Code: JP3
Contract/Grant No.: DK-15564, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine receptors and the signaling pathways to which they are coupled were examined in dispersed intestinal muscle cells. The receptors were characterized by their ability to induce contraction or relaxation, mobilize Ca2+ and stimulate or inhibit cAMP, in naive cells and in cells where only one receptor type was preserved by selective receptor protection. **Adenosine** elicited contraction and increased [Ca2+]i and cAMP; the contraction was mimicked by the A1 selective agonist, cyclopentyladenosine. A selective A1 **antagonist**, 8-cyclopentyl-1,3-dipropylxanthine, and pertussis toxin abolished contraction and the increase in [Ca2+]i and augmented the increase in cAMP. Conversely, a preferential A2 **antagonist**, 9-chloro-2-(2-furyl) [1,2,4]triazolo[1,5-c]quinazolin-5-amine augmented contraction and the increase in [Ca2+]i and abolished the increase in cAMP; a cAMP-kinase inhibitor, Rp-cAMP[S], had a similar effect, augmenting contraction and the increase in [Ca2+]i. **Adenosine** elicited also relaxation of maximally contracted cells that increased or decreased in parallel with cAMP. The selective A2a agonist, 2-p-(2-carboxyethyl)phenethylamino-5'-N-ethylcarboxamido **adenosine**, was a very weak relaxant agent, and the selective A2a **antagonist**, 8-(3-chlorostyryl)caffeine, had no effect on **adenosine**-induced relaxation. In cells where only A1 receptors were preserved, the cAMP response to **adenosine** was abolished, although contraction and [Ca2+]i were increased to the same extent as when naive cells were treated with the A2 **antagonist**. Conversely, in cells where only A2 receptors were preserved, contraction and the increase in [Ca2+]i were abolished and the increase in cAMP was augmented to the same level as when naive cells were treated with the A1 **antagonist**.(ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/80 (Item 80 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08463627 95136452 PMID: 7834835
Adenosine A2a and **A2b** receptors in cultured fetal chick heart cells. High- and low-affinity coupling to stimulation of myocyte contractility and cAMP accumulation.
Liang BT; Haltiwanger B
Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.
Circulation research (UNITED STATES) Feb 1995, 76 (2) p242-51, ISSN 0009-7330 Journal Code: DAJ
Contract/Grant No.: RO1-HL-48225, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine exerts pronounced biological effects in the heart cell.

The role of multiple **adenosine** receptor subtypes in regulating the heart cell function is not known. Ventricular cells cultured from chick embryos 14 days in ovo were used to study a novel feature of heart cell regulation by the stimulatory **adenosine** receptors. The inhibitory **adenosine** A1 receptor pathway was first inactivated by pertussis toxin treatment of the cultures, and the effects of **adenosine** agonists and antagonists on the heart cell contractile amplitude, measured via an opticovideo motion detection system, and on the modulation of cAMP level were determined. **Adenosine** and N-ethyladenosine-5'-uronic acid (NECA), capable of activating both the **adenosine** A2a and **A2b** receptors, caused a greater increase in the contractile amplitude than did the A2a-selective agonist 2-[4-(2-carboxythyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine (CGS21680). NECA caused a biphasic increase in cAMP, which became monophasic in the presence of the A2a receptor-selective **antagonist** 8-(3-chlorostyryl)caffeine, whereas the CGS21680-induced cAMP response was monophasic. Blocking with 8-(3-chlorostyryl)caffeine abolished most of the CGS21680-elicited contractile or cAMP response while attenuating only part of the **adenosine**- or NECA-stimulated responses. Blocking with the **A2b**-selective antagonists 1,3-diethyl-8-phenylxanthine or alloxazine caused a more pronounced inhibititon of the contractile or cAMP response by **adenosine** or NECA than by CGS21680. Affinity of the A2a receptor was 60-fold higher than that of the **A2b** receptor. These data demonstrate that a functional **A2b** receptor is expressed on the heart cell and is capable of mediating augmentation of cardiac myocyte contractility and that **adenosine** A2a and **A2b** receptors, with greatly different affinity, coexist and are coupled to the same functional responses. Taken together, the data suggest a novel feature of heart cell regulation, where the high-affinity A2a receptor can play an important modulatory role in the presence of a low level of **adenosine**, whereas the low-affinity **A2b** receptor becomes functionally important when the **adenosine** level is high.

2/3,AB/81 (Item 81 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08449897 95162465 PMID: 7858863
Failure of CGS15943A to block the hypotensive action of agonists acting at the **adenosine** A3 receptor.
Patel M; Sheehan MJ; Strong P
Glaxo Research and Development Ltd., Ware, Herts.
British journal of pharmacology (ENGLAND) Nov 1994, 113 (3) p741-8, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. **Adenosine** receptor agonists were evaluated for their activity at the putative **adenosine** A3 receptor which mediates a 'xanthine-resistant' hypotensive response in the anaesthetized rat. The compounds tested were: the A1/A3 receptor agonist, N-[2-(4-aminophenyl)ethyl]**adenosine** (APNEA), the non-selective **adenosine** receptor agonist, 5'-N-ethylcarboxamidoadenosine (NECA), the **adenosine** A1 receptor-selective agonists, N-[(1S,trans)-2-hydroxy cyclopentyl]**adenosine** (GR79236) and N6-cyclopentyl **adenosine** (CPA), the A2a receptor-selective agonists, 2-[[2-[4-(2-carboxyethyl) phenyl] ethyl] amino]-N- ethylcarboxamidoadenosine (CGS21680) and 2-phenylaminoadenosine (CV1808), and the moderately **A2b** selective agonist, N-[(2-methylphenyl)methyl]**adenosine** (metrifudil). 2. In confirmation of literature findings, APNEA (1-1000 nmol kg-1) induced hypotension and bradycardia; the hypotension was not blocked by pretreatment with the xanthine **antagonist**, 8-P-sulphophenyltheophylline (8-sPT; 40 mg kg-1, i.v.), whereas the bradycardia was attenuated. The non-xanthine **antagonist**, 9-fluoro-2-(2-furyl)-5,6-dihydro [1,2,4]triazolo[1,5-c]- quinazin-5-imine (CGS15943A; 3 mg kg-1 i.v.), also attenuated the bradycardia without affecting the hypotension. 3. The

adenosine A1 receptor-selective agonists, GR79236 and CPA, both produced dose-dependent falls in blood pressure and heart rate which were antagonized by 8-sPT (40 mg kg-1) and CGS15943A (3 mg kg-1). 4. The **adenosine** A2a receptor-selective agonists, CGS21680 and CV1808, produced only a hypotensive response which was antagonized by 8-sPT (40 mg kg-1) and to a much greater extent by CGS15943A (3 mg kg-1), consistent with the response being mediated solely by A2a receptors.(ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/82 (Item 82 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08440042 95017671 PMID: 7932201
The endothelium of the rat renal artery plays an obligatory role in A2 **adenosine** receptor-mediated relaxation induced by 5'-N-ethylcarboxamidoadenosine and N6-cyclopentyladenosine.
Martin PL; Potts AA
Department of Pharmacology, Whitby Research, Inc., Richmond, Virginia.
Journal of pharmacology and experimental therapeutics (UNITED STATES) Sep 1994, 270 (3) p893-9, ISSN 0022-3565 Journal Code: JP3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Studies were undertaken in the rat isolated renal artery in order to determine if **adenosine** receptor agonists were capable of inducing the release of nitric oxide from the renovascular endothelium. N6-cyclopentyladenosine (CPA) and 5'-N-ethylcarboxamidoadenosine (NECA) produced concentration-dependent relaxations in endothelium intact renal artery rings. The NECA curve was biphasic with a first phase pA50 of 6.05. The CPA curve was monophasic with a pA50 of 4.35. In the absence of endothelium the curves to both NECA and CPA were monophasic with pA50 values of 3.37 and 3.50, respectively. The A2a **adenosine** receptor-selective agonist CGS21680 (2-[p-(2-carboxyethyl)-phenethylamino]-5'-N-ethylcarboxamidoadenosine) was inactive in endothelium intact tissues. Relaxant responses to CPA and NECA in the presence of endothelium were antagonized by 8-p-sulfophenyltheophylline and by 1,3-dipropyl-8-cyclopentylxanthine only at a nonselective concentration (3 x 10(-6) M) suggesting activation of A2 **adenosine** receptors. The responses to CPA and NECA in the absence of endothelium are not due to activation of A1 or A2 **adenosine** receptor subtypes because they are resistant to blockade by these xanthines. CPA and NECA responses in the presence of endothelium were inhibited by NG-nitro-L-arginine methylester (L-NAME), a nitric oxide synthase inhibitor, but not by the cyclooxygenase inhibitor indomethacin or the K+ATP channel **antagonist** glibenclamide. These results suggest that the rat renal artery contains **A2b** **adenosine** receptors that are located exclusively on the endothelium and cause the release of nitric oxide.

2/3,AB/83 (Item 83 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08417276 94374489 PMID: 8088373
KF17837 ((E)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-7-methylxanthine), a potent and selective **adenosine** A2 receptor **antagonist**.
Nonaka H; Ichimura M; Takeda M; Nonaka Y; Shimada J; Suzuki F; Yamaguchi K; Kase H
Pharmaceutical Research Laboratories, Kyowa hakko Kogyo Co., Ltd, Shizuoka, Japan.
European journal of pharmacology (NETHERLANDS) May 17 1994, 267 (3) p335-41, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

8-(3,4-Dimethoxystryryl)-1,3-dipropyl-7-methylxanthine exhibited high affinity and selectivity for **adenosine** A2A receptors in binding assay using rat striatal A2A receptors labeled with [3H]2-[p-(2-carboxyethyl)-phenethylamino]-5'-N-ethylcarboxamido adenosin e (CGS21680). The affinity was stereo selective: the E isomer, KF17837, showed a Ki value of 1.0 +/- 0.057 nM for the A2A receptors, whereas the Z isomer showed much lower affinity. KF17837 had 62-fold selectivity for the A2A receptors versus rat forebrain A1 receptors labeled with [3H]N6-cyclohexyladenosine (CHA). KF17837 was rapidly photoisomerized to form a stable equilibrium mixture (18% E - 82% Z), KF17837S, which showed Ki values of 7.9 +/- 0.055 nM and 390 +/- 68 nM for the A2A and A1 receptors, respectively. The inhibition type was competitive for [3H]CGS21680 binding. In rat pheochromocytoma PC12 cells KF17837S antagonized cAMP accumulation induced by 1 microM CGS21680 via the A2A receptors, with an IC50 value of 53 +/- 10 nM. cAMP accumulation induced by 10 microM 5'-N-ethylcarboxamidoadenosine via the **A2B** receptors in Jurkat cells (human T-cell line) was inhibited by KF17837S with an IC50 value of 1500 +/- 290 nM. These results indicate that KF17837S (and hence KF17837) is a highly potent and selective **adenosine** A2A receptor **antagonist**.

2/3,AB/84 (Item 84 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

0841076 94282448 PMID: 8012696

Adenosine A2B -receptor-mediated cyclic AMP accumulation in primary rat astrocytes.

Peakman MC; Hill SJ
Department of Physiology & Pharmacology, Medical School, Queen's Medical Centre, Nottingham.

British journal of pharmacology (ENGLAND) Jan 1994, 111 (1) p191-8, ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

1. The effects of **adenosine** receptor agonists and antagonists on the accumulation of cyclic AMP have been investigated in primary cultures of rat astrocytes. 2. **Adenosine** A2-receptor stimulation caused a concentration-dependent increase in the accumulation of [3H]-cyclic AMP in cells prelabelled with [3H]-adenine. The rank order of agonist potencies was 5'-N-ethylcarboxamidoadenosine (NECA; EC50 = 1 microM) > **adenosine** (EC50 = 5 microM) > 2-chloroadenosine (EC50 = 20 microM) >> CGS 21680 (EC50 > 10 microM). The presence of 0.5 microM dipyridamole, an **adenosine** uptake blocker, had no effect on the potency of **adenosine**. 3. The response to 10 microM NECA was antagonized in a concentration-dependent manner by the non-selective **adenosine** receptor antagonists, xanthine amine congener (apparent KD = 12 nM), PD 115,199 (apparent KD = 134 nM) and 8-phenyltheophylline (apparent KD = 126 nM). However, the A1-receptor-selective **antagonist**, 8-cyclopentyl-1,3-dipropylxanthine, had no significant effect on the responses to NECA or 2-chloroadenosine at concentrations up to 1 microM. 4. Stimulation of A1-receptors with the selective agonist, N6-cyclopentyladenosine, did not alter the basal accumulation of [3H]-cyclic AMP but inhibited a forskolin-mediated elevation of [3H]-cyclic AMP accumulation by a maximal value of 42%. This inhibition was fully reversed in the presence of 0.1 microM, 8-cyclopentyl-1,3-dipropylxanthine. 5. The time course for NECA-mediated [3H]-cyclic AMP accumulation was investigated. The results suggest that there is a substantial efflux of cyclic AMP from the cells in addition to the rapid and sustained elevation of intracellular cyclic AMP (5 fold over basal) which was also observed. 6. These data indicate that rat astrocytes in primary culture express an **A2B-adenosine** receptor coupled positively to adenylyl cyclase. Furthermore, the presence of A1-receptors negatively coupled to adenylyl cyclase appears to have no significant effect on the **A2B** -receptor-mediated cyclic AMP responses to NECA and 2-chloroadenosine.

2/3,AB/85 (Item 85 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08359951 95195960 PMID: 7889296
Characterization of the **adenosine** receptors mediating hypothermia in the conscious mouse.
Anderson R; Sheehan MJ; Strong P
Department of Cellular Sciences, Glaxo Research and Development Ltd., Ware, Hertfordshire.
British journal of pharmacology (ENGLAND) Dec 1994, 113 (4) p1386-90 , ISSN 0007-1188 Journal Code: B00
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The effects of a range of **adenosine** receptor-selective ligands on body temperature were investigated following intracerebroventricular (i.c.v.) and intraperitoneal (i.p.) injection in conscious mice. The compounds tested were the non-selective **adenosine** receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA), the **adenosine** A1 receptor-selective agonists cyclopentyl-**adenosine** (CPA), N6-(9R-phenyl-isopropyl)-**adenosine** (R-PIA) and N-(1S,trans)-[2-hydroxycyclopentyl]-**adenosine** (GR79236), the A2a receptor selective agonist 2-[p-(2-carboxyethyl)phenethylamino]-5'-N-ethylcarboxyamidoadenosine (CGS-21680), the **A2b** receptor agonist N-[(2-methylphenyl)methyl[**adenosine** (metrifudil) and the A3 receptor agonist N6-(4-aminophenylethyl)**adenosine** (APNEA). 2. NECA (0.01-1 microgram, i.c.v.), all of the A1-selective agonists (0.01-1 microgram, i.c.v.) and APNEA (0.1-3 micrograms i.c.v.) produced profound and dose-related hypothermia and sedation. However, CGS-21680 (0.1-10 micrograms i.c.v.) and metrifudil (0.01-1 microgram i.c.v.), produced only mild hypothermia at the highest doses tested. 3. The hypothermic response to the A1 receptor-selective agonists, GR79236 and R-PIA was dose-dependently antagonized by peripheral administration of either the non-selective **adenosine** receptor **antagonist** , 8-phenyltheophylline (8-PT, approximately 40 and 30 fold rightward shifts of the dose-response curves respectively at 10 mg kg-1, i.p.), or the **adenosine** A1 receptor-selective **antagonist** , 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, approximately 20 fold shift of the GR79236 dose-response curve at 1 mg kg-1, i.p.). The hypothermic response to APNEA was similarly dose-dependently antagonized by the A1 receptor-selective **antagonist**, DPCPX (5 fold shift at 0.1 mg kg-1, i.p.).(ABSTRACT TRUNCATED AT 250 WORDS)

2/3,AB/86 (Item 86 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08299568 95080091 PMID: 7988413
Localization and characterization of **adenosine** receptor expression in rat testis.
Pivkees SA
Herman B Wells Center for Pediatric Research, Section of Pediatric Endocrinology, James Whitcomb Riley Hospital for Children, Indiana University Medical School, Indianapolis 46202.
Endocrinology (UNITED STATES) Dec 1994, 135 (6) p2307-13, ISSN 0013-7227 Journal Code: EGZ
Contract/Grant No.: HD-00942, HD, NICHD
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Adenosine has long been suspected to play an important role in regulating male reproduction. To determine the sites of **adenosine** action in testis, the distribution of a family of recently cloned **adenosine** receptors was examined in rats. Northern blot analysis and

in situ hybridization studies revealed high levels of testicular A3 **adenosine** receptor messenger RNA and lower levels of A1 **adenosine** receptor messenger RNA. Neither A2a nor **A2b** **adenosine** receptor gene expression could be detected. In situ hybridization and comparative polymerase chain reaction studies showed high level A3 receptor gene expression in germ cells (spermatocytes and spermatids), whereas high levels of A1 receptor gene expression was seen in Sertoli cells. To test for the presence of functional A1 and A3 receptors, the regulation of adenylyl cyclase by **adenosine** analogs was examined in seminiferous tubules and spermatozoa. Treatment of seminiferous tubules with forskolin resulted in a 5-fold increase in cAMP levels. The A1/A3 receptor agonist iodo-N6-aminobenzyladenosine inhibited forskolin-stimulated cAMP levels in the presence of the A1 8-cyclopentyl-1,3-dipropylxanthine **antagonist** 8-cyclopentyl-1,3-dipropylxanthine, showing that functional A3 receptors were present. The A1-selective agonist N6-cyclopentyladenosine also inhibited forskolin-stimulated cAMP levels, showing that functional A1 receptors were present. Treatment of spermatozoa with forskolin resulted in a 2-fold increase in cAMP levels. However, neither iodo-N6-aminobenzyladenosine nor N6-cyclopentyladenosine altered basal or forskolin-stimulated cAMP levels in sperm. These data show that functional inhibitory **adenosine** receptors are widely distributed in testis, with different patterns of expression.

2/3,AB/87 (Item 87 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08081280 94067052 PMID: 8246918
Multiple mechanisms for desensitization of A2a **adenosine** receptor-mediated cAMP elevation in rat pheochromocytoma PC12 cells.
Chern Y; Lai HL; Fong JC; Liang Y
Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China.
Molecular pharmacology (UNITED STATES) Nov 1993, 44 (5) p950-8, ISSN 0026-895X Journal Code: NGR
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To understand the regulation of A2a **adenosine** receptor (A2a-R) response, we examined the molecular mechanisms underlying the desensitization of A2a response in rat pheochromocytoma PC12 cells, which possess an A2a-R identical with the A2a receptor we recently cloned from rat brain. Prolonged exposure of PC12 cells to **adenosine** agonists significantly inhibited the response of the cells to subsequent stimulation with an A2a-selective **adenosine** agonist (CGS21680). No significant change in the number of binding sites and affinity for CGS21680 was observed in desensitized cells, nor did we find any significant change in the transcript level of A2a-R in cells pretreated with **adenosine** agonists. However, the basal adenylyl cyclase activity and the cyclase activities stimulated by **adenosine** agonists, by GTP gamma S, and by forskolin were reduced in desensitized cells. Prolonged exposure of PC12 cells to dibutyryl-cAMP did not significantly change either the basal or the **adenosine** agonist-evoked adenylyl cyclase activity. Therefore, elevation of cellular cAMP content is by itself not sufficient to produce the observed reductions of adenylyl cyclase activity with A2a desensitization. Inhibition of adenylyl cyclase activity in desensitized cells occurred after short-term (30 min) incubation with CGS21680 and could be blocked by the **adenosine antagonist** 8-cyclopentyl-1,3-dipropylxanthine. Gs alpha protein levels did not significantly change after a 30-min exposure to CGS21680. In contrast, long-term exposure (12-20 hr) of PC12 cells to **adenosine** agonists resulted in a slight further reduction of adenylyl cyclase activity and a consistent decline in the Gs alpha protein level. In addition, long-term incubation with **adenosine** agonists or with forskolin-enhanced phosphodiesterase (PDE) activity in the cytosolic and membrane fractions by 57 +/- 9% and 53 +/- 18%, respectively.

Hydrolysis of cAMP was significantly faster in agonist-desensitized cells than in control cells. PDE might therefore play an important role in desensitization of the A2a response in PC12 cells. Polymerase chain reaction-based analysis of the mRNA for A2a-R and **A2b**-R indicated that both A2a-R and **A2b**-R were present in PC12 cells; the **A2b** response was also diminished in A2a-desensitized cells. Our data suggest that inhibition of adenylyl cyclase after short-term agonist treatment, down-regulation of Gs alpha protein level after long-term agonist treatment, and activation of PDE after long-term agonist treatment account for desensitization of the A2a-mediated response in PC12 cells.

2/3,AB/88 (Item 88 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08033541 93233003 PMID: 8474010
2-Phenylethoxy-9-methyladenine: an **adenosine** receptor **antagonist** that discriminates between A2 **adenosine** receptors in the aorta and the coronary vessels from the guinea pig.
Martin PL; Ueeda M; Olsson RA
Department of Pharmacology, Whitby Research, Inc., Richmond, Virginia.
Journal of pharmacology and experimental therapeutics (UNITED STATES) Apr 1993, 265 (1) p248-53, ISSN 0022-3565 Journal Code: JP3
Language: ENGLISH
Document type: Journal Article
Record type: Completed
Substituting a methyl group for the ribose moiety of N6-substituted adenosines that are selective agonists at the **adenosine** A1 receptor creates antagonists that are A1-selective. Inasmuch as 2-phenylethoxyadenosine is a selective agonist for the **adenosine** A2 receptor, 2-phenylethoxy-9-methyl-adenine (PEMA) was synthesized and tested as a potential **adenosine** A2 receptor **antagonist**. In guinea pig hearts, PEMA antagonized with the same potency (pKB approximately 6.1) the A1-mediated negative dromotropic and inotropic actions and the A2-mediated coronary vasoactivity of the nonselective **adenosine** receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA). PEMA at concentrations up to 30 microM did not antagonize the NECA-induced relaxations in guinea pig aortic rings. At concentrations exceeding 10 microM, PEMA caused xanthine-insensitive relaxations of both the aorta and the coronary vessels. Pharmacological resultant analysis revealed A2 receptor antagonism by PEMA in the guinea pig aorta (pKB = 5.2). The nonselective **adenosine** receptor **antagonist** 8-p-sulfophenyl-theophylline antagonized NECA responses in all four assays with equal potency (pKB approximately 5.7). Thus, PEMA does not discriminate between A2 receptors in the coronary vessels and A1 receptors in the atria of the guinea pig, but it is 30-fold more potent at antagonizing the A2 receptor in coronaries than the A2 receptors in the aorta. The data suggest that the A2 receptors in the coronary vasculature may be of the A2a subtype, whereas those in the aorta may be of the **A2b** subtype.

2/3,AB/89 (Item 89 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07954441 94052163 PMID: 8234299
Molecular cloning and characterization of the human A3 **adenosine** receptor.
Salvatore CA; Jacobson MA; Taylor HE; Linden J; Johnson RG
Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Nov 1 1993, 90 (21) p10365-9, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: HL37942, HL, NHLBI
Language: ENGLISH

Document type: Journal Article
Record type: Completed

The human A3 **adenosine** receptor was cloned from a striatal cDNA library using a probe derived from the homologous rat sequence. The cDNA encodes a protein of 318 amino acids and exhibits 72% and 85% overall identity with the rat and sheep A3 **adenosine** receptor sequences, respectively. Specific and saturable binding of the **adenosine** receptor agonist N6-(4-amino-3-[125I]iodobenzyl)**adenosine** [125I]ABA was measured on the human A3 receptor stably expressed in Chinese hamster ovary cells with a Kd = 10 nM. The potency order for **adenosine** receptor agonists was N-ethylcarboxamidoadenosine (NECA) > or = (R)-N6-phenyl-2-propyladenosine [(R)-PIA] > N6-cyclopentyladenosine (CPA) > (S)-N6-phenyl-2-propyladenosine [(S)-PIA]. The human receptor was blocked by xanthine antagonists, most potently by 3-(3-iodo-4-aminobenzyl)-8-(4-oxy acetate)phenyl-1-propylxanthine (I-ABOPX) with a potency order of I-ABOPX > 1,3-dipropyl-8-(4-acrylate)phenylxanthine > or = xanthine amino congener >> 1,3-dipropyl-8-cyclopentylxanthine. **Adenosine** , NECA, (R)- and (S)-PIA, and CPA inhibited forskolin-stimulated cAMP accumulation by 30-40% in stably transfected cells; I-ABA is a partial agonist. When measured in the presence of antagonists, the dose-response curves of NECA-induced inhibition of forskolin-stimulated cAMP accumulation were right-shifted. **Antagonist** potencies determined by Schild analyses correlated well with those established by competition for radioligand binding. The A3 **adenosine** receptor transcript is widespread and, in contrast to the A1, A2a, and **A2b** transcripts, the most abundant expression is found in the lung and liver. The tissue distribution of A3 mRNA is more similar to the widespread profile found in sheep than to the restricted profile found in the rat. This raises the possibility that numerous physiological effects of **adenosine** may be mediated by A3 **adenosine** receptors.

2/3,AB/90 (Item 90 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07809014 93011535 PMID: 1397010
Relative agonist potencies of C2-substituted analogues of **adenosine** : evidence for **adenosine A2B** receptors in the guinea pig aorta.
Martin EL
Department of Pharmacology, Whitby Research, Inc., Richmond, VA 23220.
European journal of pharmacology (NETHERLANDS) Jun 5 1992, 216 (2) p235-42, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Nine C2-substituted **adenosine** analogues that are potent and selective for the A2-**adenosine** receptor were tested for their ability to induce relaxations of the guinea pig aorta. Compounds tested were 2-phenylethoxyadenosine (PEA), 2-phenylethoxy-5'-N-ethylcarboxamidoadenosine (PENECA), 2-cyclohexylethoxyadenosine (CEA), 2-fluorophenylethoxyadenosine (FPEA), 2-methoxyphenylethoxyadenosine (MPEA), 2-naphthylethoxyadenosine (NEA), 2-phenylaminoadenosine (CV-1808), 2-phenylethylaminoadenosine (PEAA) and 2-carboxyethylphenethylamino-5'-N-ethylcarboxamidoadenosine (CGS21680). The responses to these agents were compared to those of three standard **adenosine** receptor agonists, 5'-N-ethylcarboxamidoadenosine (NECA), N6-cyclohexyladenosine (CHA) and R-N6-phenylisopropyladenosine (R-PIA). The C2-ethoxyadenosine analogues were 30- to 140-fold less potent than NECA and the C2-amino-substituted analogues were 250 to 1000-fold less potent than NECA at inducing relaxations of the guinea pig aorta. All of the analogues were also less potent than the A1-selective agonist R-PIA. However, only responses to NECA were competitively antagonized by the non-selective **adenosine** receptor **antagonist** 8-phenyltheophylline (8-PT), pKB = 6.83 +/- 0.05. The results suggest that the C2-substituted analogues produce relaxations of the guinea pig aorta through a combination of actions at A2-**adenosine** receptors and at xanthine resistant sites. The lack of potency of these analogues at activating the xanthine sensitive

A2-receptors in the guinea pig aorta suggests that these **adenosine** receptors may be of the **A2b**-subtype.

2/3,AB/91 (Item 91 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07807492 92392387 PMID: 1325798
Molecular cloning and expression of an **adenosine A2b** receptor from human brain.
Pierce KD; Furlong TJ; Selbie LA; Shine J
Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, N.S.W., Australia.
Biochemical and biophysical research communications (UNITED STATES) Aug 31 1992, 187 (1) p86-93, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A novel receptor cDNA was isolated from a human hippocampal cDNA library. The encoded polypeptide contains structural features consistent with its classification as a G protein-coupled receptor and shares 45% homology with the human A1 and A2a **adenosine** receptors. Chinese hamster ovary K1 cells expressing this receptor showed marked stimulation of adenylate cyclase when treated with 1mM **adenosine**. There was no response to ligands selective for A1 and A2a receptors but the general **adenosine** agonist N-ethylcarboxyamidoadenosine (NECA) caused a 10 fold increase in cyclic AMP accumulation with an EC50 of approximately 0.9 microM. This effect was inhibited by the **adenosine** receptor **antagonist** theophylline. Specific binding of A1 and A2a selective agonists and NECA was not detected. It is proposed that the novel receptor is a human brain **adenosine A2b** receptor subtype.

2/3,AB/92 (Item 92 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07617014 92332030 PMID: 1628877
Further evidence that propentofylline (HWA 285) influences both **adenosine** receptors and **adenosine** transport.
Fredholm BB; Fastbom J; Kvanta A; Gerwins P; Parkinson F
Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.
Fundamental & clinical pharmacology (FRANCE) 1992, 6 (3) p99-111, ISSN 0767-3981 Journal Code: F8S
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have examined the actions of a novel xanthine derivative, propentofylline (HWA 285), that has been shown to protect against ischemic brain damage in rats and gerbils, on **adenosine** receptors (A1 and A2), and on **adenosine** transporters using several techniques, cells and tissues. Propentofylline and its hydroxylated metabolite A 72 0287 were about 20 times less potent than theophylline in displacing A1-agonist binding to membranes from rat cortex, and A1-**antagonist** binding to whole DDT, MF-2 smooth muscle cells. A1-agonist binding to **adenosine** A1-receptors in several brain structures was inhibited in a concentration-dependent manner by A 72 0287 and propentofylline as judged by quantitative autoradiography (IC50-values 300-600 microM in eg striatum and in cortex layer IV). In two functional assays, A1-receptor mediated effects were blocked by propentofylline. A1-receptor-mediated inhibition of cyclic AMP accumulation was virtually abolished by 100 microM propentofylline. The A1-receptor-mediated inhibition of evoked acetylcholine release was also reduced by propentofylline, but in this case the effect is not due exclusively to **adenosine** receptor antagonism but also to another action since the presynaptic inhibitory effect of carbachol was also inhibited. **Adenosine** A2-receptors were also

antagonized by propentofylline as judged by a concentration-dependent antagonism of A2-agonist-induced cAMP accumulation in human T-leukemia cells (possessing putative **A2b** -receptors; pA2-value 180 microM compared to 0.26 microM for 8-cpt), and in PC-12 cells (possessing putative A2a-receptors, Ki-value 365 microM). Finally, **adenosine** transporters were affected by propentofylline and A 72 0287. Thus, [3H]-nitrobenzylthioinosine-binding to guinea-pig cardiac membranes was blocked by propentofylline or A 72 0287 (Ki 270 microM). The present results show that propentofylline and its hydroxylated metabolite can influence **adenosine** mechanisms in a multitude of ways. How these different actions may contribute to the ability of propentofylline to reduce the magnitude of ischemic damage is discussed.

2/3,AB/93 (Item 93 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07460074 92008250 PMID: 1915589
Carbamazepine distinguishes between **adenosine** receptors that mediate different second messenger responses.
Van Calker D; Steber R; Klotz KN; Greil W
Psychiatric Hospital, University of Munich, F.R.G.
European journal of pharmacology (NETHERLANDS) Apr 25 1991, 206 (4) p285-7, ISSN 0014-2999 Journal Code: EN6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The mechanism of the therapeutic and prophylactic effects of carbamazepine (CBZ) in affective psychoses is unknown but may in part be related to the potent competitive interaction of CBZ with **adenosine** -binding sites in the brain. The anticonvulsant and sedative properties of CBZ are reminiscent of the effects evoked by **adenosine**-agonists and contrast sharply with the opposite actions of **adenosine**-antagonists like caffeine. However, indirect evidence suggests an **antagonist**- rather than an agonist-like activity of CBZ at **adenosine**-receptors. We have used various model systems, in which **adenosine** receptor subtypes mediate different second messenger-responses, to investigate this-apparent paradox. CBZ was found to antagonize the A1-receptor-mediated inhibition of cyclic AMP accumulation in cultured astroblasts and in GH3-cells. Furthermore, CBZ also inhibits the **adenosine**-induced increase in the level of cyclic AMP in cultured astroblasts, which is mediated by low-affinity **A2b** -receptors. In contrast, CBZ does not block the inhibition elicited by **adenosine** -agonists of the agonist induced increased formation of inositolphosphates in human neutrophils, which is mediated by high-affinity A2a-receptors. The specific antagonism by CBZ of A1- but not of high-affinity A2a-receptors was further supported by binding experiments using rat brain membranes. These results suggest that the paradox of CBZ's antagonistic effects at **adenosine** -receptors might be at least partially reconciled by a selective antagonistic action of CBZ at A1 receptors but not at high-affinity A2a-receptors.

2/3,AB/94 (Item 94 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07131282 93124074 PMID: 8380444
Endogenous **adenosine** regulates the apparent efficacy of 1-aminocyclopentyl-1S,3R-dicarboxylate inhibition of forskolin-stimulated cyclic AMP accumulation in rat cerebral cortical slices.
Cartmell J; Kemp JA; Alexander SP; Kendall DA
Department of Physiology and Pharmacology, University of Nottingham Medical School, Queen's Medical Centre, U.K.
Journal of neurochemistry (UNITED STATES) Feb 1993, 60 (2) p780-2, ISSN 0022-3042 Journal Code: JAV

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

In rat cerebral cortical slices, the 1-aminocyclopentyl-1S,3R-dicarboxylate (1S,3R-ACPD) isomer of the selective metabotropic excitatory amino acid agonist ACPD inhibited forskolin-stimulated cyclic AMP (cAMP) accumulation in a concentration-dependent manner with a maximal inhibition of 51 +/- 3% and a half-maximally effective concentration of 8.8 +/- 3.4 microM. Similarly, 1R,3S-ACPD inhibited the forskolin response in a concentration-dependent manner, but with an inhibition of 80 +/- 5% at 3 mM. In addition to inhibiting forskolin-stimulated cAMP levels, 1S,3R-ACPD, but not 1R,3S-ACPD, enhanced the cAMP response to **A2b adenosine** receptor activation. In the presence of 1.2 U/ml of **adenosine** deaminase (included to reduce the contribution of endogenous **adenosine**), the efficacy of 1S,3R-ACPD was increased (88 +/- 3% inhibition), but the potency was unchanged. The **adenosine** receptor **antagonist** 8-cyclopentyl-1,3-dipropylxanthine also increased the inhibitory effect of 100 microM 1S,3R-ACPD, from 57 +/- 1 to 78 +/- 5%. These results indicate that endogenous **adenosine** plays an important role in regulating the apparent efficacy of 1S,3R-ACPD inhibition of forskolin-stimulated cAMP accumulation in rat cerebral cortical slices and that previous studies in rat hippocampus and hypothalamus in the absence of added **adenosine** deaminase may have underestimated the efficacy of this compound.

2/3,AB/95 (Item 95 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

0673693 91101627 PMID: 1987452

Characterization of the binding of a novel nonxanthine **adenosine** **antagonist** radioligand, [3H]CGS 15943, to multiple affinity states of the **adenosine** A1 receptor in the rat cortex.

Jarvis MF; Williams M; Do UH; Sills MA

Research Department, CIBA-GEIGY Corp., Summit, New Jersey.

Molecular pharmacology (UNITED STATES) Jan 1991, 39 (1) p49-54, ISSN 0026-895X Journal Code: NGR

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The triazoloquinazoline CGS 15943 is the first reported nonxanthine **adenosine** **antagonist** that has high affinity for brain **adenosine** receptors. In the present study, the binding of [3H] CGS 15943 to recognition sites in rat cortical membranes was characterized. Saturation experiments revealed that [3H]CGS 15943 labeled a single class of recognition sites with high affinity (Kd = 4 nM) and limited capacity (Bmax = 1.5 pmol/mg of protein). Competition studies revealed that the binding of [3H]CGS 15943 was consistent with the labeling of brain **adenosine** A1 receptors. **Adenosine** agonists inhibited 1 nM [3H]CGS 15943 binding with the following order of activity N6-cyclopentyladenosine (IC50 = 15 nM) greater than 2-chloroadenosine greater than (R)-N6-phenylisopropyladenosine greater than 5'-N6-ethylcarboxamidoadenosine greater than (S)N6-phenylisopropyladenosine greater than CGS 21680 greater than CV 1808 (IC50 greater than 10,000 nM). The potency order for **adenosine** antagonists was CGS 15943 (IC50 = 5 nM) greater than 8-phenyltheophylline greater than 1,3-dipropyl-8-(4-amino-2-chloro)phenylxanthine greater than 1,3-diethyl-8-phenylxanthine greater than theophylline = caffeine (IC50 greater than 10,000 nM). **Antagonist** inhibition curves were steep and best described by a one-site binding model. In contrast, **adenosine** A1 agonist competition curves were shallow, as indicated by Hill coefficients less than unity. Computer analysis revealed that these inhibition curves were best described by a two-site binding model. Agonist competition curves generated in the presence of 1 mM GTP resulted in a rightward shift and steepening of the inhibition-concentration curves, whereas **antagonist** binding was not

altered in the presence of GTP. The complex binding interactions found with **adenosine** agonists indicate that [3H]CGS 15943 labels both high and low affinity components of the **adenosine** A1 receptor in the rat cortex. Additionally, the present data also provide some evidence that [3H]CGS 15943 may also recognize an additional low affinity binding component, which may represent a putative low affinity **A2b** receptor in this tissue.

2/3,AB/96 (Item 1 from file: 5)
DIALOG File 5:Biosis Previews(R)
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13230643 BIOSIS NO.: 200100437792
Functional characterization of coronary vascular **adenosine** receptors in the mouse.
AUTHOR: Flood Amanda; Headrick John P(a)
AUTHOR ADDRESS: (a)National Heart Foundation Research Centre, School of Health Science, Griffith University, Southport, QLD, 4217: j.headrick@mailbox.gu.edu.au**Australia
JOURNAL: British Journal of Pharmacology 133 (7):p1063-1072 August, 2001
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1 Coronary responses to **adenosine** agonists were assessed in perfused mouse and rat hearts. The roles of nitric oxide (NO) and ATP-dependent K+ channels (KATP) were studied in the mouse. 2 Resting coronary resistance was lower in mouse vs rat, as was minimal resistance (2.2+-0.1 vs 3.8+-0.2 mmHg ml-1 min-1 g-1). Peak hyperaemic flow after 20-60 s occlusion was greater in mouse. 3 **Adenosine** agonists induced coronary dilation in mouse, with pEC50s of 9.4+-0.1 for 2-(p-(2-carboxyethyl)phenethylamino)-5'-N-ethyl carboxamidoadenosine (CGS 1680, A2A-selective agonist), 9.3+-0.1 for 5'-N-ethylcarboxamidoadenosine (NECA, A1/A2 agonist), 8.4+-0.1 for 2-chloroadenosine (A1/A2 agonist), 7.7+-0.1 for N6-(R)-(phenylisopropyl) **adenosine** (R-PIA, A1/**A2B** selective), and 6.8+-0.2 for **adenosine**. The potency order (CGS21680 = NECA > 2-chloroadenosine > R-PIA > **adenosine**) supports A2A **adenosine** receptor-mediated dilation in mouse coronary vessels. 0.2-2 muM of the **A2B**-selective **antagonist** alloxazine failed to alter CGS21680 or 2-chloroadenosine responses. 4 pEC50s in rat were 6.7+-0.2 for CGS21680, 7.3+-0.1 for NECA, 7.6+-0.1 for 2-chloroadenosine, 7.2+-0.1 for R-PIA, and 6.2+-0.1 for **adenosine** (2-chloroadenosine > NECA = R-PIA > CGS21680 > **adenosine**), supporting an **A2B adenosine** receptor response. 5 NO-synthase antagonism with 50 muM NG-nitro L-arginine (L-NOARG) increased resistance by apprx25%, and inhibited responses to CGS21680 (pEC50=9.0+-0.1), 2-chloroadenosine (pEC50=7.3+-0.2) and endothelial-dependent ADP, but not sodium nitroprusside (SNP). KATP channel blockade with 5 muM glibenclamide increased resistance by apprx80% and inhibited responses to CGS21680 in control (pEC50=8.3+-0.1) and L-NOARG-treated hearts (pEC50=7.3+-0.1), and to 2-chloroadenosine in control (pEC50=6.7+-0.1) and L-NOARG-treated hearts (pEC50=5.9+-0.2). 6 In summary, mouse coronary vessels are more sensitive to **adenosine** than rat vessels. A2A **adenosine** receptors mediate dilation in mouse coronary vessels vs **A2B** receptors in rat. Responses in the mouse involve a sensitive NO-dependent response and KATP-dependent dilation.

2001

2/3,AB/97 (Item 2 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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13218147 BIOSIS NO.: 200100425296
Proliferation, migration, and ERK activation in human retinal endothelial cells through **A2B adenosine** receptor stimulation.
AUTHOR: Grant Maria B(a); Davis Margaret I; Caballero Sergio; Feoktistov Igor; Biaggioni Italo; Belardinelli Luiz
AUTHOR ADDRESS: (a)Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL, 32610-0267: grantma@pharmacology.ufl.edu** USA
JOURNAL: IOVS 42 (9):p2068-2073 August, 2001
MEDIUM: print
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: PURPOSE: The nucleoside **adenosine** has been implicated in angiogenesis. A previous study demonstrated that activation of the **A2B adenosine** receptor (AdoR) increases cAMP accumulation, cell proliferation, and VEGF expression in human retinal endothelial cell (HRECs). In the present study, the role of this receptor was further characterized by examination of the effects of the selective **A2B** AdoR antagonists 3-N-propylxanthine (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX) on AdoR-mediated HREC proliferation, capillary tube formation, and signal-transduction pathways. METHODS: HRECs were exposed to the **adenosine** analogue 5'-N-ethylcarboxamido-**adenosine** (NECA) in the absence or presence of AdoR antagonists. Migration was measured using Boyden chambers. Proliferation was assessed by counting cells. Western analysis was used to assess extracellular signal-related kinase (ERK) and cAMP response element-binding protein (CREB) in cell lysates. The effect of AdoR activation on tube formation was studied using cells grown on a synthetic basement membrane matrix. RESULTS: NECA induced proliferation in a concentration-dependent manner that was inhibited by enprofylline and IPDX. NECA stimulated chemotaxis in a concentration-dependent manner that was also blocked by both **A2B** AdoR antagonists. NECA activated ERK and CREB in HRECs. Both **A2B** AdoR antagonists diminished activation of ERK by NECA exposure. ERK activation was also blocked by the ERK-mitogen-activated protein kinase (MAPK) inhibitor PD98059, but not by the protein kinase A (PKA) inhibitor H-89. CREB activation was blocked by H-89, but not by PD98059, suggesting that ERK activation is independent of PKA. NECA enhanced tube formation on the matrix, whereas both **A2B** AdoR antagonists attenuated this effect. CONCLUSIONS: The selective **A2B** AdoR antagonists, enprofylline and IPDX, inhibited NECA-stimulated proliferation, ERK activation, cell migration, and capillary tube formation. **A2B** AdoR inhibition may offer a way to inhibit retinal angiogenesis and provide a novel therapeutic approach to treatment of diseases associated with aberrant neovascularization, such as diabetic retinopathy and retinopathy of prematurity.

2001

2/3,AB/9 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13209845 BIOSIS NO.: 200100416994
Reversal of the antiinflammatory effects of methotrexate by the nonselective **adenosine** receptor antagonists theophylline and caffeine: Evidence that the antiinflammatory effects of methotrexate are mediated via multiple **adenosine** receptors in rat adjuvant arthritis.

AUTHOR: Montesinos M Carmen; Yap Josephine S; Desai Avani; Posadas Inmaculada; McCrary Christine T; Cronstein Bruce N(a)
AUTHOR ADDRESS: (a)Department of Medicine, Division of Rheumatology, New York University Medical Center, 550 First Avenue, New York, NY, 10016** USA
JOURNAL: Arthritis & Rheumatism 43 (3):p656-663 March, 2000
MEDIUM: print
ISSN: 0004-3591
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Objective. Weekly low-dose methotrexate (MTX) remains the mainstay of second-line therapy for rheumatoid arthritis (RA). We have previously reported that **adenosine**, acting at specific receptors on inflammatory cells, mediates the antiinflammatory effects of MTX in both in vitro and in vivo models of acute inflammation, but the mechanism by which MTX suppresses the chronic inflammation of arthritis remains controversial. The present study was undertaken to further investigate the means by which **adenosine** mediates the antiinflammatory effects of MTX. Methods. The effects of 2 nonselective **adenosine** receptor antagonists, theophylline and caffeine, were examined, using the rat adjuvant arthritis model of RA. These agents were given alone and in conjunction with MTX, and arthritis severity was assessed clinically, radiologically, and histologically. Since rodent **adenosine** A3 receptors are not blocked by theophylline, selective A1, A2A, and **A2B** receptor antagonists were tested as well. Results. Control animals developed severe arthritis, which was markedly attenuated by weekly treatment with MTX (0.75 mg/kg/week). Neither theophylline alone nor caffeine alone (each at 10 mg/kg/day) significantly affected the severity of the arthritis, but both agents markedly reversed the effect of MTX as measured by a severity index, hindpaw swelling, and hindpaw ankylosis. Radiographic and histologic analyses confirmed these observations. Neither A1, A2A, nor **A2B** receptor antagonists affected the capacity of MTX to ameliorate inflammation in adjuvant arthritis. Conclusion. These results provide strong evidence that **adenosine** mediates the antiinflammatory effects of MTX in this model of RA. Moreover, the findings suggest that abstinence from caffeine, a ubiquitous food additive and medication, may enhance the therapeutic effects of MTX in RA.

2000

2/3,AB/9 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13123714 BIOSIS NO.: 200100330883
Structural predictions of **adenosine** 2B **antagonist** affinity using molecular field analysis.
AUTHOR: Song Yuqing; Coupar Ian M; Iskander Magdy N(a)
AUTHOR ADDRESS: (a)Department of Medicinal Chemistry, Victorian College of Pharmacy, Monash University, 381 Royal Parade, Parkville, VIC, 3052: magdy.iskander@vcp.monash.edu.au**Australia
JOURNAL: Quantitative Structure-Activity Relationships 20 (1):p23-30 May, 2001
MEDIUM: print
ISSN: 0931-8771
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 3D structural evaluation of the **adenosine** 2B (**A2B**) **antagonist** binding site is the major aim for developing specific selective antagonists. In an attempt to deduce structural properties of the **antagonist** site, a pharmacophore model was developed using 85 known **A2B** antagonists. The molecular mechanics optimization methods were used to deduce the likely binding conformations of the antagonists at the binding site. Super-imposition of the antagonists was carried out using fit-atoms. This alignment was used to develop CoMFA models of the **A2B antagonist** binding site. The models possessed promising predictive ability as indicated by the high cross-validated correlation (q2=0.732, r2=0.982) and the prediction on the external test set. The analyses showed that steric and electrostatic interactions contributed to **A2B antagonist** biological activity equally. The hydrogen-bond donor nature of the 7-position of xanthine (1apprx68) and 3-position of alloxazine (83) was essential for the biological activity. In addition, the presence of more negative charges on the 1-N position of xanthine and 10-N position of alloxazine increases biological activity. The bulky aromatic substitutions on the 8-position of xanthine compounds improve activity, while an alkyl substitution on the 1-position of alloxazine might enhance activity. The model generated from this investigation produced important structural requirements, which will be used to optimize the structural complementarity of the antagonists at the **A2B** binding site.

2001

2/3,AB/100 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13117815 BIOSIS NO.: 200100324964
Differential effects of UTP, ATP, and **adenosine** on ciliary activity of human nasal epithelial cells.
AUTHOR: Morse Diane M; Smullen Jennifer L; Davis C William(a)
AUTHOR ADDRESS: (a)Univ. of North Carolina, 6009 Thurston-Bowles, Chapel Hill, NC, 27599-7248: cwdavis@med.unc.edu**USA
JOURNAL: American Journal of Physiology 280 (6 Part 1):pC1485-C1497 June, 2001
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The purinergic regulation of ciliary activity was studied using small, continuously superfused explants of human nasal epithelium. The P2Y2 purinoceptor (P2Y2-R) was identified as the major purinoceptor regulating ciliary beat frequency (CBF); UTP (EC50=4.7 muM), ATP, and **adenosine**-5'-O-(3-thiotriphosphate) elicited similar maximal responses, approximately twofold over baseline. ATP, however, elicited a post-peak sustained plateau in CBF (1.83+-0.1-fold), whereas the post-peak CBF response to UTP declined over 15 min to a low-level plateau (1.36+-0.16-fold). UDP also stimulated ciliary beating, probably via P2Y6-R, with a maximal effect approximately one-half that elicited by P2Y2-R stimulation. Not indicated were P2Y1-R-, P2Y4-R-, or P2Y11-R-mediated effects. **A2B**-receptor agonists elicited sustained responses in CBF approximately equal to those from UTP/ATP (5'-(N-ethylcarboxamido)**adenosine**, EC50=0.09 muM; **adenosine**, EC50=0.7 muM). Surprisingly, ADP elicited a sustained stimulation in CBF. The ADP effect and the post-peak sustained portion of the ATP response in CBF were inhibited by the A2-R **antagonist** 8-(p-sulfophenyl)theophylline. Hence, ATP affects ciliary activity through P2Y2-R and, after an apparent ectohydrolysis to **adenosine**,

through A2BAR.

2001

2/3,AB/101 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13114003 BIOSIS NO.: 200100321152
A2B adenosine receptor mediates proliferation, migration, and activation of ERK in human retinal endothelial cells.
AUTHOR: Caballero S(a); Davis M I(a); Grant M B(a)
AUTHOR ADDRESS: (a)Pharmacology and Therapeutics, University of Florida, Gainesville, FL**USA
JOURNAL: IOVS 42 (4):pS244 March 15, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

2/3,AB/102 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13094876 BIOSIS NO.: 200100302025
Regulation of VEGF gene expression by **adenosine**. Role of G proteins.
AUTHOR: Feoktistov Igor(a); Goldstein Anna E(a); Biaggioni Italo(a)
AUTHOR ADDRESS: (a)Vanderbilt University, 348 MRB II, Nashville, TN, 37232 **USA
JOURNAL: FASEB Journal 15 (4):pA580 March 7, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** released by hypoxic tissues may contribute to angiogenesis. It has been previously shown that **A2B adenosine** receptors, coupled to both Gs and Gq, stimulated production of vascular endothelial growth factor (VEGF) in human retinal endothelial cells (Grant et al., Circ Res. 1999;85:699-706). In this study we examined regulation of VEGF gene expression by **adenosine** in human microvascular endothelial cells (HMEC-1). The non-selective agonist NECA stimulated cAMP accumulation with an EC50 of 2 muM increasing its intracellular levels 11.2 +- 0.5 fold. The selective A2A agonist CGS 21680, 10 muM, increased cAMP only 2.6 +- 0.7 fold. Furthermore, the selective **A2B antagonist** IPDX, 10 muM, attenuated the NECA-induced cAMP generation to 3.7 +- 0.5 fold. Thus, HMEC-1 cells express both A2A and **A2B** receptors. HMEC-1 cells were cotransfected with mutationally activated alpha subunits of Gq or Gs proteins, or with an empty expression vector (mock transfection) together with a luciferase reporter under control of the human VEGF promoter. Stimulation of HMEC-1 with 100 muM NECA for six hours increased reporter activity by 41 +- 6% compared with nonstimulated cells. Luciferase activity in cells cotransfected with active alphaq was increased 14.2 +- 0.5 fold compared with mock-transfected cells. In contrast, constitutively active alphas

decreased, if any, the basal VEGF reporter activity by 28 +- 17%. Cotransfection of HMEC [redacted] with constitutively active Ras [redacted] sulted in 22.8 +- 1.3 fold increase in luciferase activity compared wi[redacted] mock-transfected cells. Our data indicate that stimulation of Gq and Ras (both thought to be linked to **A2B**), but not Gs (coupled to both A2A and **A2B** receptors) increase VEGF gene expression.

2001

2/3,AB/10 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13089893 BIOSIS NO.: 200100297042
Discovery of new antagonists of the **adenosine A2B** receptor.
AUTHOR: Webb Thomas R(a); Lvovskiy Dmitriy(a); Melman N; Ji X; Linden J; Jacobson Kenneth A
AUTHOR ADDRESS: (a)ChemBridge Corporation, 16981 Via Tazon, Suite G, San Diego, CA, 92127**USA
JOURNAL: Abstracts of Papers American Chemical Society 221 (1-2):pMEDI 30 2001
MEDIUM: print
CONFERENCE/MEETING: 221st National Meeting of the American Chemical Society San Diego, California, USA April 01-05, 2001
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2001

2/3,AB/11 (Item 9 from file: 5)
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13083830 BIOSIS NO.: 200100290979
Adenosine receptor signaling in vitro and in vivo.
AUTHOR: Fredholm Bertil B(a); Arslan Giulia; Halldner Linda; Kull Bjorn; Schulte Gunnar; Aden Ulrika; Svenningsson Per
AUTHOR ADDRESS: (a)Department of Physiology and Pharmacology, Karolinska Institutet, S-171 77, Stockholm: bertil.fredholm@fyfa.ki.se**Sweden
JOURNAL: Drug Development Research 52 (1-2):p274-282 Jan-Feb, 2001
MEDIUM: print
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DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: This overview will focus on recent data from our laboratory. The four cloned human **adenosine** receptors stably transfected into Chinese hamster ovary cells were studied with respect to signaling via cyclic AMP and mitogen-activated protein (MAP) kinases. **Adenosine** acted as a full agonist at all the **adenosine** receptors when increases (A2A or **A2B** receptors) or decreases (A1 and A3 receptors) in cyclic AMP accumulation were studied. **Adenosine** was approximately equipotent at A1, A2A, and A3 receptors, but approximately 50 times higher concentrations were needed at **A2B** receptors. The potency of **adenosine** was such that levels encountered under basal physiological conditions (30-300 nM) were sufficient to activate all but the **A2B** receptors. Inosine was a low-efficacy agonist at A1 and A3 receptors but was inactive at A2A and **A2B** receptors. Thus, **adenosine** is the most important agonist and the only one at A2A and **A2B** receptors. When MAP kinase signaling was examined,

adenosine was equipotent at all the four receptors, and significant activation was noted at [redacted]00 nM **adenosine**. The potency of **adenosine** is dependent not only on the type of receptor but also on receptor number. Thus, high potency of **adenosine** is seen only where the receptor is expressed abundantly. These and other results are reviewed and discussed in relation to agonist and **antagonist** effects in vivo. In particular, we summarize recent data that show that **adenosine** tonically activates A2A receptors in the basal ganglia. Some aspects of the use of **adenosine** A2A receptor antagonists in the treatment of Parkinson disease also are highlighted.

2001

2/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13082318 BIOSIS NO.: 200100289527
Pyrazolo(4,3-e)1,2,4-triazolo(1,5-c)pyrimidine derivatives: A new pharmacological tool for the characterization of the human A3 **adenosine** receptor.
AUTHOR: Baraldi Pier Giovanni(a); Cacciari Barbara; Romagnoli Romeo; Spalluto Giampiero; Varani Katia; Gessi Stefania; Merighi Stefania; Borea Pier Andrea
AUTHOR ADDRESS: (a)Dipartimento di Scienze Farmaceutiche, Via Fossato di Mortara 17-19, I-44100, Ferrara: pgb@dns.unife.it**Italy
JOURNAL: Drug Development Research 52 (1-2):p406-415 Jan-Feb, 2001
MEDIUM: print
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** regulates many physiological functions by interaction with four different G-protein-coupled receptors classified as A1, A2A, **A2B**, and A3. While **adenosine** A1 and A2A receptor subtypes have been pharmacologically characterized through the use of selective ligands, the **A2B** and A3 **adenosine** receptor subtypes are presently under study in order to better understand their physio-pathological functions. In particular, activation of **adenosine** A3 receptors has been shown to stimulate phospholipase C and D and to inhibit adenylate cyclase. Activation of A3 **adenosine** receptors also causes the release of inflammatory mediators such as histamine from mast cells, which are responsible for processes such as inflammation and hypotension. For these reasons, it has been suggested that A3 **adenosine** receptor antagonists can be considered potential drugs for the treatment of asthma and inflammation. In the last few years different classes of heterocyclic compounds have been identified as A3 **adenosine** antagonists, but none of the tested compounds showed significant selectivity for A3 **adenosine** receptor subtype. Herein, we report our recent results on a class of pyrazolo(4,3-e)1,2,4-triazolo(1,5-c)pyrimidine derivatives as a new class of potent and selective human A3 **adenosine** receptor antagonists. The full characterization of the first high-affinity radioligand **antagonist** for this receptor subtype, designated (3H) MRE3008F20, is briefly summarized.

2001

2/3,AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13082376 BIOSIS NO.: [redacted]00289525
Adenosine A2A receptor ligands: Effects on neuronal excitability.
AUTHOR: Phillis John W(a)
AUTHOR ADDRESS: (a)Department of Physiology, Wayne State University School of Medicine, 540 E. Canfield, Detroit, MI, 48201-1928: jphillis@med.wayne.edu**USA
JOURNAL: Drug Development Research 52 (1-2):p331-336 Jan-Feb, 2001
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ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Our evolving understanding of the mechanisms involved in the actions of **adenosine** on central neurons during the course of the past three decades has largely been a consequence of certain specific advances. Early recognition that **adenosine** could either inhibit or stimulate cyclic AMP formation led to the concept of A1 (inhibitory) or A2 (stimulatory) receptors coupled via G proteins to adenylate cyclase. The early development of selective agonists and antagonists for the A1 binding site then stimulated a considerable volume of pharmacological research on the actions of this receptor. Evidence for the existence of more than one type of A2 receptor also accumulated, culminating in the cloning of two receptors, the high-affinity A2A and lower-affinity **A2B** receptors. The synthesis and availability of CGS 21680, a selective agonist for the A2A receptor, made possible studies on the pharmacological effects of its activation and the subsequent development of a series of A2A receptor antagonists has further clarified the roles that this receptor plays in the central nervous system. Whereas A1 receptor activation inhibits synaptic transmission, primarily by decreasing excitatory neurotransmitter release from presynaptic nerve terminals, A2A receptor stimulation appears to enhance neurotransmitter release as a result of increased Ca2+ uptake. In brain slices, CGS 21680 facilitates excitatory transmission by increasing glutamate and acetylcholine release. However, when tested in vivo on central neurons by iontophoretic application, CGS 21680 has had a powerful depressant effect on neuronal activity which was blocked by coapplication of an A2A receptor **antagonist** but not by a selective A1 receptor **antagonist**. Further studies with the GABAA antagonists bicuculline and picrotoxin, which also block the inhibitory actions of CGS 21680, revealed that in this instance A2A receptor activation facilitates GABA release, causing inhibition of neuronal firing. Whether the GABA release is a consequence of enhanced excitatory drive to GABAergic neurons or is a direct effect of an action at A2A receptors on GABAergic nerve terminals remains uncertain.

2001

2/3,AB/10? (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13048342 BIOSIS NO.: 200100255491
Adenosine A2A and **A2B** receptors-mediated hyperpolarization in porcine coronary artery endothelial cells.
AUTHOR: Olanrewaju Hammed A(a); Gafurov Boris S(a); Lieberman Edward M(a); Mustafa Jamal S(a)
AUTHOR ADDRESS: (a)Brody School of Medicine, East Carolina University, Moye Blvd., Greenville, NC, 27858**USA
JOURNAL: FASEB Journal 15 (5):pA763 March 8, 2001
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies

for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Background/Aim: **Adenosine** is a potent vasodilator in most vascular beds of mammals and an important modulator of cardiac function. It has been postulated that the endothelium may have a role in vascular actions of **adenosine**. However, the role of endothelial cells in the **adenosine** (presumably A2A and **A2B** receptors) mediated increase in resting membrane potential (RMP) still remains unclear. We investigated the effects of **adenosine** agonists (NECA, CGS-21680, CAD) and its **antagonist**, ZM-241385, a selective A2A **adenosine** receptor **antagonist** on the RMP of confluent monolayers of cultured porcine coronary artery endothelial cells (PCAEC). Methods: Conventional microelectrode methods were used to measure PCAEC membrane potentials. Results: The average amplitude histogram of the resting membrane potential (RMP) was -32 +- 1.2 mV. **Adenosine** agonists at 10-5 M elicited significant increase in RMP. NECA (10-5M) caused a significant increase in RMP compared to CGS 21680 and CAD at similar concentration. Furthermore, ZM-241385 at 10-5M significantly inhibited the hyperpolarizing effect of CGS-21680 and CAD but only partly the effect of NECA, suggesting the presence of both A2A and **A2B** receptors. Also, NECA significantly ($P< 0.05$) increased RMP compared to CGS 21680 at similar concentration, again supporting a role for A2A and **A2B** **adenosine** receptors in **adenosine**-mediated hyperpolarization in PCAEC. Conclusion: These results provide additional evidence for the presence of A2A and **A2B** **adenosine** receptors in PCAEC, which may play an important role in the regulation of vascular tone.

2001

2/3,AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13000014 BIOSIS NO.: 200100207163
A2B receptors mediate the antimitogenic effects of **adenosine** in cardiac fibroblasts.
AUTHOR: Dubey Raghvendra K(a); Gillespie Delbert G; Zacharia Lefteris C; Mi Zaichuan; Jackson Edwin K
AUTHOR ADDRESS: (a)Department of Obstetrics and Gynecology, Clinic for Endocrinology, Frauenklinik, University Hospital Zurich, D215, NORD-1, 8091, Zurich: raghvendra.dubey@fhk.usz.ch**Switzerland
JOURNAL: Hypertension (Baltimore) 37 (2 Part 2):p716-721 February, 2001
MEDIUM: print
ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** inhibits growth of cardiac fibroblasts; however, the **adenosine** receptor subtype that mediates this antimitogenic effect remains undefined. Therefore, the goals of this study were to determine which **adenosine** receptor subtype mediates the antimitogenic effects of **adenosine** and to investigate the signal transduction mechanisms involved. In rat left ventricular cardiac fibroblasts, PDGF-BB (25 ng/mL) stimulated DNA synthesis (3H-thymidine incorporation), cellular proliferation (cell number), collagen synthesis (3H-proline incorporation), and MAP kinase activity. The **adenosine** receptor agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine,

but not N6-cyclopentyladenosine, 4-aminobenzyl-5'-N-methylcarboxamidoadenosine, or CGS21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an **A2B** receptor-mediated effect. The **adenosine** receptor antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an **antagonist** profile consistent with an A2 receptor-mediated effect. Antisense, but not sense or scrambled, oligonucleotides to the **A2B** receptor stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and collagen synthesis. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of **adenosine** deaminase and **adenosine** kinase, respectively) were abolished by antisense, but not scrambled or sense, oligonucleotides to the **A2B** receptor. Our findings strongly support the hypothesis that **adenosine** causes inhibition of CF growth by activating **A2B** receptors coupled to inhibition of MAP kinase activity. Thus, **A2B** receptors may play a critical role in regulating cardiac remodeling associated with CF proliferation. Pharmacologic or molecular biological activation of **A2B** receptors may prevent cardiac remodeling associated with hypertension, myocardial infarction, and myocardial reperfusion injury after ischemia.

2001

2/3,AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12992571 BIOSIS NO.: 200100199720
MRS 1754, a selective **A2B adenosine** receptor **antagonist**, inhibits degranulation of cultured human but not murine mast cells.
AUTHOR: Kirshenbaum Arnold S(a); Hettinger Barbara; Day Yuayn-Ji; Gilfillan Alasdair M(a); Metcalfe Dean D(a); Kim Yong-Chul(a); Linden Joel; Jacobson Kenneth A(a)
AUTHOR ADDRESS: (a)NIH, Bethesda, MD**USA
JOURNAL: Journal of Allergy and Clinical Immunology 107 (2):pS281 February, 2001
MEDIUM: print
CONFERENCE/MEETING: 57th Annual Meeting of the American Academy of Allergy, Asthma and Immunology New Orleans, Louisiana, USA March 16-21, 2001
ISSN: 0091-6749
RECORD TYPE: Citation
LANGUAGE: English
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2001

2/3,AB/15 (Item 15 from file: 5)
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12966995 BIOSIS NO.: 200100174144
Effect of an **adenosine** A1 receptor agonist and a novel pyrimidoindole on membrane properties and neurotransmitter release in rat cortical and hippocampal neurons.
AUTHOR: Eschke D; Brand A; Scheibler P; Hess S; Eger K; Allgaier C; Nieber K(a)
AUTHOR ADDRESS: (a)Institute of Pharmacy, University of Leipzig, Bruederstrasse 34, D-04103, Leipzig: nieber@rz.uni-leipzig.de**Germany
JOURNAL: Neurochemistry International 38 (5):p391-398 April, 2001
MEDIUM: print
ISSN: 0197-0186

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RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Activation of **adenosine** A1 receptors by endogenous **adenosine** plays a neuroprotective role under various pathophysiological conditions including hypoxia. Intracellular recordings were made in rat pyramidal cells of the somatosensory cortex. Hypoxia (5 min) induced a membrane depolarization and a decrease of input resistance. The A1 receptor agonist N6-cyclopentyladenosine (CPA, 100 muM) reversibly inhibited the hypoxic depolarization. The inhibition was also present after blockade of the A2A, **A2B** and A3 receptor subtypes by selective antagonists. CPA had no effect on the hypoxic decrease of input resistance. 1,3-Dipropyl-8-cyclopentylxanthine (DPCPX), a selective A1 receptor **antagonist**, which did not alter hypoxic depolarization when given alone abolished the inhibitory effect of CPA. Neither CPA nor DPCPX influenced membrane potential or apparent input resistance under normoxic conditions. The novel pyrimidoindole (R)-(-)-(1-methylbenzyl)-2-(4'-pyridyl)-9H-pyrimido(4,5-b)indole-4-amine (APPPI, 1 and 10 muM) reversibly diminished hypoxic depolarization but had no significant effect on input resistance. The effect of APPPI at a concentration of 1 muM, but not at 10 muM, was blocked by DPCPX (0.1 muM). CPA (100 muM) inhibited (3H)-noradrenaline ((3H)-NA) release from rat hippocampal brain slices significantly only in the presence of rauwolscine (0.1 muM), an alpha2-adrenoceptor **antagonist**. APPPI (1 and 10 muM) exhibited an inhibitory effect similar to that observed with CPA. The effects of both CPA and APPPI were antagonized by DPCPX (0.1 muM). The present data suggest that mainly presynaptic mechanisms prevent neurons from hypoxic changes by an inhibition of transmitter release. However, in contrast to CPA, APPPI exhibited additional effects, which require further investigation.

2001

2/3,AB/111 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12902408 BIOSIS NO.: 200100109557
Adenosine A2a-receptor autoradiography in the rat brain.
AUTHOR: DeMet E M(a); Chicz-DeMet A
AUTHOR ADDRESS: (a)Mental Health Care Group, VAMC Long Beach, CA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-7402 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** plays a key role in the regulation of tissue oxygenation, neuronal firing, and neurotransmitter release. Two basic types of **adenosine** receptors, A1- and A2-, have opposing actions on many systems. The A2 receptor type is further divided into high-affinity A2a and low-affinity **A2b** subtypes. The A1 and **A2b** subtypes are widely distributed in brain. In contrast, A2a receptors are closely associated with, and act as modulators of, dopaminergic D2 receptors. Therefore, A2a antagonists are of interest as potential antiparkinsonian agents whereas A2a agonists are of interest as possible antipsychotics. Research on A2a receptors has been hampered by a lack of specific

ligands. The present study describes an autoradiographic procedure which is based upon 3H-ZM241[redacted], a potent and selective A2a a[redacted]gonist. Nonspecific binding was assessed in the presence of 100 uM 5'-N-ethyl carboxamide **adenosine** (NECA). Specific binding was largely restricted to the striatum, was saturable (Bmax=1086 fmol/mg), and was 9 fold greater than nonspecific binding at Kd=1.5 nM. The present results indicate that this procedure is suitable for the study of drug actions on A2a receptor kinetics.

2000

2/3,AB/112 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12871158 BIOSIS NO.: 200100078307
Pyrazolo(4,3-e)1,2,4-triazolo(1,5-c)pyrimidine derivatives as highly potent and selective human A3 **adenosine** receptor antagonists: Influence of the chain at the N8 pyrazole nitrogen.
AUTHOR: Baraldi Pier Giovanni(a); Cacciari Barbara; Romagnoli Romeo; Spalluto Giampiero; Moro Stefano; Klotz Karl-Norbert; Leung Edward; Varani Katia; Gessi Stefania; Merighi Stefania; Borea Pier Andrea
AUTHOR ADDRESS: (a)Dipartimento di Scienze Farmaceutiche, Universita degli Studi di Ferrara, Via Fossato di Mortara 17-19, I-44100, Ferrara: pgb@dns.unife.it**Italy
JOURNAL: Journal of Medicinal Chemistry 43 (25):p4768-4780 December 14, 2000
MEDIUM: print
ISSN: 0022-2623
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: An enlarged series of pyrazolotriazolopyrimidines previously reported, in preliminary form (Baraldi et al. J. Med. Chem. 1999, 42, 4473-4478), as highly potent and selective human A3 **adenosine** receptor antagonists is described. The synthesized compounds showed A3 **adenosine** receptor affinity in the sub-nonomolar range and high levels of selectivity evaluated in radioligand binding assays at human A1, A2A, **A2B**, and A3 **adenosine** receptors. In particular, the effect of the chain at the N8 pyrazole nitrogen was analyzed. This study allowed us to identify the derivative with the methyl group at the N8 pyrazole combined with the 4-methoxyphenylcarbamoyl moiety at the N5 position as the compound with the best binding profile in terms of both affinity and selectivity (hA3 = 0.2 nM, hA1/hA3 = 5485, hA2A/hA3 = 6950, hA2B/hA3 = 1305). All the compounds proved to be full antagonists in a specific functional model where the inhibition of cAMP generation by IB-MECA was measured in membranes of CHO cells stably transfected with the human A3 receptor. The new compounds are among the most potent and selective A3 antagonists so far described. The derivatives with higher affinity at human A3 **adenosine** receptors proved to be antagonists, in the cAMP assay, capable of inhibiting the effect of IB-MECA with IC50 values in the nanomolar range, with a trend strictly similar to that observed in the binding assay. Also a molecular modeling study was carried out, with the aim to identify possible pharmacophore maps. In fact, a sterically controlled structure-activity relationship was found for the N8 pyrazole substituted derivatives, showing a correlation between the calculated molecular volume of pyrazolo(4,3-e)1,2,4-triazolo(1,5-c)-pyrimidine derivatives and their experimental Ki values.

2000

2/3,AB/113 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12849479 BIOSIS NO.: 200100056628
7-deazaadenines bearing polar substituents: Structure-activity relationships of new A1 and A3 **adenosine** receptor antagonists.
AUTHOR: Hess Sonja(a); Mueller Christa E; Frobenius Wolfram; Reith Ulrike; Klotz Karl-Norbert; Eger Kurt
AUTHOR ADDRESS: (a)Pharmaceutical Chemistry, Institute of Pharmacy, University of Leipzig, Bruederstrasse 34, D-04103, Leipzig: hess@rz.uni-leipzig.de**Germany
JOURNAL: Journal of Medicinal Chemistry 43 (24):p4636-4646 November 30, 2000
MEDIUM: print
ISSN: 0022-2623
DOCUMENT TYPE: Article
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: A series of 28 new pyrrolo(2,3-d)pyrimidine-4-amines, pyrimido(4,5-b)indole-4-amines, and tetrahydropyrimido(4,5-b)indole-4-amines was synthesized and their **adenosine** receptor affinity determined in radioligand binding assays at rat A1 and A2A **adenosine** receptors (ARs). Selected compounds were additionally investigated in binding assays at recombinant A3 ARs. The 2-phenyl residue in (R)-7-(1-methylbenzyl)-2-phenylpyrrolo(2,3-d)pyrimidine-4-amine (ADPEP, 1) and in the corresponding pyrimido(4,5-b)indole (APEPI, 3) could be bioisosterically replaced by heterocyclic rings, such as 2-thienyl and 4-pyridyl. The resulting compounds retained high affinity and selectivity for A1 ARs. Judging from the investigation of selected compounds, it appears that they are also potent at human A1 ARs and selective not only versus A2A ARs but also highly selective versus **A2B** and A3 ARs. The p-pyridyl-substituted derivatives 11 and 27 (APPPI) may be interesting pharmacological tools due to their fluorescent properties. Pyrrolo-(2,3-d)pyrimidine-4-amine derivatives which were simultaneously substituted at N7 and N4, combining the substitution pattern of ADPEP (1) and DPEAP (2), showed very low affinity for A1 ARs. This finding supports our previously published hypothesis of different binding modes for pyrrolopyrimidines, such as ADPEP (1) and DPEAP (2). DPEAP (2), a pyrrolo(2,3-d)-pyrimidine-4-amine substituted at the amino group (N4), was found to exhibit high affinity for human A3 ARs (Ki = 28 nM), whereas N4-unsubstituted analogues were inactive, DPEAP (2) and related compounds provide new leads for the development of antagonists for the human A3 AR.
2000

2/3,AB/114 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12841541 BIOSIS NO.: 200100048690
Why are **A2B** receptors low-affinity **adenosine** receptors? Mutation of Asn273 to Tyr increases affinity of human **A2B** receptor for 2-(1-hexynyl)**adenosine**.
AUTHOR: Beukers Margot W(a); den Dulk Hans; van Tilburg Erica W; Brouwer Jaap; IJzerman Adriaan P
AUTHOR ADDRESS: (a)Division of Medicinal Chemistry, Gorlaeus Laboratories, Leiden/Amsterdam Center for Drug Research, Einsteinweg 55, 2300 RA, Leiden: beukers@chem.leidenuniv.nl**Netherlands
JOURNAL: Molecular Pharmacology 58 (6):p1349-1356 December, 2000
MEDIUM: print

ISSN: 0026-895X
DOCUMENT TYPE: Article
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine A2B** receptors are known as low-affinity receptors due to their modest-to-negligible affinity for **adenosine** and prototypic agonists. Despite numerous synthetic efforts, 5'-N-ethylcarboxamidoadenosine (NECA) still is the reference agonist, albeit nonselective for this receptor. In our search for higher affinity agonists, we developed decision schemes to select amino acids for mutation to the corresponding residues in the most homologous, higher affinity, human A2A receptor. One scheme exploited knowledge on sequence alignments and modeling data and yielded three residues, V11, L58, and F59, mutation of which did not affect agonist affinity. The second scheme combined knowledge on sequence alignments and mutation data and pointed to Ala12 and Asn273. Mutation of Ala12 to threonine did not affect the affinity for NECA, (R)-N6-(phenylisopropyl)**adenosine** (R-PIA), and 2Cl Ado. The affinity of the N273Y mutant for NECA and R-PIA and for the antagonists xanthine amine congener (XAC), ZM241385, and SCH58261 was also unaltered. However, this mutant had a slightly increased affinity for a 2-substituted **adenosine** derivative, CGS21680. This prompted us to investigate other 2-substituted adenosines, with selectivity and high affinity for A2A receptors. All four compounds tested had improved affinity for the N273Y receptor. Of these, 2-(1-hexynyl)**adenosine** had subnanomolar affinity for the N273Y receptor, 0.18 +- 0.10 muM, with a 61-fold affinity gain over the wt receptor. In addition, the non-NECA analog (S)-PHP **adenosine** had an affinity of 1.7 +- 0.5 muM for the wt receptor. The high affinity of (S)-PHP **adenosine** for the wt receptor suggests that further modifications at the 2-position may yield agonists with even higher affinity for **A2B** receptors.

2000

2/3,AB/115 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12838640 BIOSIS NO.: 200100045789
Method for improving insulin sensitivity using an **adenosine** receptor **antagonist**.
AUTHOR: LaNoue Kathryn F(a); Crist George H; Linden Joel M
AUTHOR ADDRESS: (a)Hershey, PA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1234 (2):pNo Pagination May 9, 2000
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Methods for improving insulin sensitivity in a patient using one or more **A2B adenosine** receptor antagonists are disclosed. These methods stimulate insulin dependent glucose uptake in muscle.

2000

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DIALOG(R)File 5:Biosis Previews(R)
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12817285 BIOSIS NO.: 200100024434

The pharmacology of nucleotide receptors on primary rat brain endothelial cells grown on a biol[redacted]al extracellular matrix: Effec[redacted]on intracellular calcium concentration.
AUTHOR: Sipos Ildiko; Domotor Eszter; Abbott N Joan; Adam-Vizi Vera(a)
AUTHOR ADDRESS: (a)Department of Medical Biochemistry, Semmelweis University, Budapest, H-1444: av@puskin.sote.hu**Hungary
JOURNAL: British Journal of Pharmacology 131 (6):p1195-1203 November, 2000
MEDIUM: print
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1 Brain capillary endothelial cells express a variety of nucleotide receptors, but differences have been reported between culture models. This study reports examination of nucleotide receptors on primary cultured rat brain capillary endothelial cells (RBCEC) grown on a biological extracellular matrix (ECM) to produce a more differentiated phenotype. 2 Fura-2 fluorescence ratio imaging was used to monitor intracellular free calcium concentration (Ca2+)i. ATP, UTP, and 2-methylthioATP (2-MeSATP) increased (Ca2+)i to similar levels, while 2-MeSADP, ADP and **adenosine** gave smaller responses. 3 Removal of extracellular calcium caused no significant change in the (Ca2+)i response to 2-MeSATP, evidence that the response was mediated by a metabotropic (P2Y) receptor. 4 All cells tested responded to ATP, UTP, 2-MeSATP and ADP, while 63% responded to **adenosine** and 50% to 2-MeSADP. No cells responded to alpha,beta-methyleneATP. Cells grown on rat tail collagen instead of ECM gave smaller and less uniform (Ca2+)i responses, suggesting that the differentiating effect of the ECM contributed to a more uniform receptor profile. 5 The (Ca2+)i response to the P2Y1-selective agonist 2-MeSADP was abolished in the presence of the subtype-selective **antagonist adenosine** 3'-phosphate 5'-phosphosulphate (PAPS). 6 The P2Y2 **antagonist** suramin completely blocked the response to ATP and inhibited the response to UTP by 66%. 7 The A1 subtype-selective **adenosine** receptor agonist N6-Cyclopentyladenosine (CPA) gave a small but characteristic (Ca2+)i response, while A2A and **A2B** subtype-selective agonists failed to generate (Ca2+)i changes. 8 The results are consistent with the presence on RBCEC of a P2Y2-like receptor coupled to phospholipase C, and a P2Y1-like receptor mobilizing intracellular Ca2+. The role of multiple nucleotide receptors in the function of the brain endothelium is discussed.

2000

2/3,Ab/[illegible] (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12482544 BIOSIS NO.: 200000236046
[3H]MRE 3008F20: A novel **antagonist** radioligand for the pharmacological and biochemical characterization of human A3 **adenosine** receptors.
AUTHOR: Varani Katia; Merighi Stefania; Gessi Stefania; Klotz Karl-Norbert; Leung Edward; Baraldi Pier Giovanni; Cacciari Barbara; Romagnoli Romeo; Spalluto Giampiero; Borea Pier Andrea(a)
AUTHOR ADDRESS: (a)Faculty of Medicine, Department of Clinical and Experimental Medicine, Pharmacology Unit, University of Ferrara, Via Fossato di Mortara 17-19, 44100, Ferrara**Italy
JOURNAL: Molecular Pharmacology 57 (5):p968-975 May, 2000
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English
SUMMARY LANGUAGE: Englis

ABSTRACT: The lack of a radiolabeled selective A3 **adenosine** receptor **antagonist** is a major drawback for an adequate characterization of this receptor subtype. This paper describes the pharmacological and biochemical characterization of the tritiated form of a new potent A3 **adenosine** receptor **antagonist**, the pyrazolo triazolo pyrimidine derivative (3H)5N-(4-methoxyphenylcarbamoyl)amino-8-propyl-2-(2-furyl)pyrazolo(4,3-e) -1,2,4-triazolo(1,5-c)pyrimidine ((3H)MRE 3008F20). (3H)MRE 3008F20 bound specifically to the human **adenosine** A3 receptor expressed in CHO cells (hA3CHO), and saturation analysis revealed a single high affinity binding site, KD = 0.80 +- 0.06 nM, with a Bmax = 300 +- 33 fmol/mg protein. This new ligand displayed high selectivity (1294-, 165-, and 2471-fold) in binding assay to human A3 versus A1, A2A, and **A2B** receptors, respectively, and binds to the rat A3 receptors with a Ki > 10 muM. The pharmacological profile of (3H)MRE 3008F20 binding to hA3CHO cells was evaluated using known **adenosine** receptor agonists and antagonists with a rank order of potency consistent with that typically found for interactions with the A3 **adenosine** receptors. In the adenylyl cyclase assay the same compounds exhibited a rank order of potency identical with that observed in binding experiments. Thermodynamic data indicated that (3H)MRE 3008F20 binding to hA3CHO is entropy- and enthalpy-driven in agreement with the typical behavior of other **adenosine** antagonists to A1 and A2A receptors. These results show that (3H)MRE 3008F20 is the first **antagonist** radioligand with high affinity and selectivity for the human A3 **adenosine** receptor and may be used to investigate the physiopathological role of A3 **adenosine** receptors.

2000

2/3,AB/118 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12444674 BIOSIS NO.: 200000198156
Anilide derivatives of an 8-phenylxanthine carboxylic congener are highly potent and selective antagonists at human **A2B adenosine** receptors.
AUTHOR: Kim Yong-Chul; Ji Xiao-duo; Melman Neli; Linden Joel; Jacobson Kenneth A(a)
AUTHOR ADDRESS: (a)NIDDK, LBC, NIH, Bldg. 8A, Rm. B1A-19, Bethesda, MD, 20892-0810**USA
JOURNAL: Journal of Medicinal Chemistry 43 (6):p1165-1172 March 23, 2000
ISSN: 0022-2623
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: No highly selective antagonists of the **A2B adenosine** receptor (AR) have been reported; however such antagonists have therapeutic potential as antiasthmatic agents. Here we report the synthesis of potent and selective **A2B** receptor antagonists. The structure-activity relationships (SAR) of 8-phenyl-1,3-di-(n-propyl)xanthine derivatives in binding to recombinant human **A2B** ARs in HEK-293 cells (HEK-**A2B**) and at other AR subtypes were explored. Various amide derivatives of 8-(4-((carboxymethyl)oxy)phenyl)-1,3-di-(n-propyl)xanthine, 4a, were synthesized. A comparison of aryl, alkyl, and aralkyl amides demonstrated that simple anilides, particularly those substituted in the para-position with electron-withdrawing groups, such as nitro, cyano, and acetyl, bind

selectively to human **A2B** receptors in the range of 1-3 nM. The unsubstituted anilide [redacted] had a Ki value at **A2B** receptor [redacted] of 1.48 nM but was only moderately selective versus human A1/A2A receptors and nonselective versus rat A1 receptors. Highly potent and selective **A2B** antagonists were a p-aminoacetophenone derivative 20 (Ki value 1.39 nM) and a p-cyanoanilide 27 (Ki value 1.97 nM). Compound 27 was 400-, 248-, and 123-fold selective for human **A2B** receptors versus human A1/A2A/A3 receptors, respectively, and 8.5- and 310-fold selective versus rat A1/A2A receptors, respectively. Substitution of the 1,3-dipropyl groups with 1,3-diethyl offered no disadvantage for selectivity, and high affinities at **A2B** receptors were maintained. Substitution of the p-carboxymethyloxy group of 4a and its amides with acrylic acid decreased affinity at **A2B** receptors while increasing affinity at A1 receptors. 1,3-Di-(cyclohexylmethyl) groups greatly reduced affinity at ARs, although the p-carboxymethyloxy derivative 9 was moderately selective for **A2B** receptors. Several selective **A2B** antagonists inhibited NECA-stimulated calcium mobilization in HEK-**A2B** cells.

2000

2/3,AB/119 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12426316 BIOSIS NO.: 200000179828
Effects of AMP derivatives on cyclic AMP levels in NG108-15 cells.
AUTHOR: Ohkubo Satoko(a); Nakanishi Hironori; Kimura Junko; Matsuoka Isao
AUTHOR ADDRESS: (a)Department of Pharmacology, School of Medicine, Fukushima Medical University, Fukushima, 960-1295**Japan
JOURNAL: British Journal of Pharmacology 129 (6):p1244-1250 March, 2000
ISSN: 0007-1188
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: 1 In NG108-15 neuroblastoma X glioma hybrid cells, ATP stimulates intracellular cyclic AMP formation, which is inhibited by both **adenosine** (P1) and P2 receptor antagonists. In the present study, we examined the effects of several AMP derivatives in NG108-15 cells and mouse neuroblastoma N18TG-2 cells. 2 **Adenosine** 2'-monophosphate (A2P), **adenosine** 3'-monophosphate (A3P) and **adenosine** 5'-phosphosulphate (A5PS) increased cyclic AMP levels with similar concentration-dependencies in NG108-15 cells. 3 Increases in cyclic AMP by ATP derivatives were inhibited by the P2 receptor **antagonist** PPADS, but not by suramin. Effects of AMP derivatives were also inhibited by P1 receptor antagonists ZM241385, XAC, DPCPX and partially by alloxazine. The ecto-nucleotidase inhibitor alpha,beta-methyleneADP was without effect. 4 In contrast, AMP derivatives did not change cyclic AMP levels in N18TG-2 cells. Accumulation of cyclic AMP in N18TG-2 cells was stimulated by **adenosine** A2 receptor agonists CGS21680 and NECA, but not by ATP or beta,gamma-methyleneATP, agonists for cyclic AMP production in NG108-15 cells. 5 Reverse transcription-coupled polymerase chain reaction (RT-PCR) analyses revealed that N18TG-2 cells express both A2A and **A2B** receptors, while NG108-15 cells express mainly A2A receptors. 6 AMP derivatives did not affect the P2X and P2Y receptors expressed in NG108-15 cells. 7 These results suggest that A2P, A3P and A5PS act as agonists for cyclic AMP production and that these compounds are valuable tools for determinating the mechanism of ATP-stimulated cyclic AMP response in NG108-15 cells.

2000

2/3,AB/120 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12395998 BIOSIS NO.: 200000149500
Water-soluble phosphate prodrugs of 1-propargyl-8-styrylxanthine derivatives, A2A-selective **adenosine** receptor antagonists.
AUTHOR: Sauer Roland; Maurinsh Juris; Reith Ulrike; Fuelle Friederike; Klotz Karl-Norbert; Mueller Christa E(a)
AUTHOR ADDRESS: (a)Pharmazeutische Chemie Poppelsdorf, Pharmazeutisches Institut, Kreuzbergweg 26, D-53115, Bonn**Germany
JOURNAL: Journal of Medicinal Chemistry. 43 (3):p440-448 Feb. 10, 2000
ISSN: 0022-2623
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Water-soluble prodrugs of potent, A2A-selective **adenosine** receptor (AR) antagonists were prepared. 8-(m-Bromostyryl)-3,7-dimethyl-1-propargylxanthine (BS-DMPX, 11) and the analogous 8-(m-methoxystyryl)xanthine derivative (MS-DMPX, 5b) were used as starting points. It was found that polar functional groups suitable for the attachment of a prodrug moiety were tolerated on the styryl ring and even better on the 3-substituent. 8-(m-Hydroxystyryl)-DMPX (7) and 3-(3-hydroxypropyl)-8-(m-methoxystyryl)-1-propargylxanthine (5e, MSX-2) were the most potent and A2A-selective compounds and were selected for prodrug formation. For the preparation of 5e a new ring-closure method was applied. Treatment of 6-amino-1-(3-hydroxypropyl)-5-(m-methoxycinnamoylamino)-3-propargyluracil with hexamethyldisilazane at high temperature resulted in higher yields of the target xanthine than the standard ring-closure procedure using sodium hydroxide. Phosphate prodrugs were prepared by classical phosphorylation using phosphorus oxychloride and alternatively by using a phosphoramidite method. Phosphates of the aliphatic alcohol 5e could be obtained by both methods in similar yields. The phenolic compound 7, however, could be phosphorylated only by using the phosphoramidite method. The disodium salts of the phosphate prodrugs exhibited high water solubility (8-(m-methoxystyryl)-7-methyl-3-(3-O-phosphatylpropyl)-1-propargylxanthine disodium salt, 9b: 17 mM, 9 mg/mL). Prodrug 9b was found to be stable in aqueous solution (pH 7) but readily cleaved by phosphatases to liberate 5e (MSX-2). Compound 5e showed high affinity for rat A2A AR (Ki = 8 nM), human recombinant A2A AR (Ki = 5 nM), and human native A2A AR (Ki = 15 nM) and was highly selective versus rat A1 AR (110-fold), human recombinant A2A AR (500-fold), human **A2B** AR (>2000-fold), and human A3 AR (>2100-fold).

2000

2/3,AB/121 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12368160 BIOSIS NO.: 200000121662
A2B receptors mediate antimitogenesis in vascular smooth muscle cells.
AUTHOR: Dubey Raghvendra K(a); Gillespie Delbert G; Shue Holly; Jackson Edwin K
AUTHOR ADDRESS: (a)Center for Clinical Pharmacology, University of Pittsburgh Medical Center, 200 Lothrop St, 623 Scaife Hall, Pittsburgh, PA, 15213-2582**USA
JOURNAL: Hypertension (Baltimore) 35 (1 Part 2):p267-272 Jan., 2000

ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** inhibits growth of vascular smooth muscle cells. The goals of this study were to determine which **adenosine** receptor subtype mediates the antimitogenic effects of **adenosine** and to investigate the signal transduction mechanisms involved. In rat aortic vascular smooth muscle cells, platelet-derived growth factor-BB (PDGF-BB) (25 ng/mL) stimulated DNA synthesis ((3H)thymidine incorporation), cellular proliferation (cell number), collagen synthesis ((3H)proline incorporation), total protein synthesis ((3H)leucine incorporation), and mitogen-activated protein (MAP) kinase activity. The **adenosine** receptor agonists 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, but not N6-cyclopentyladenosine or CGS21680, inhibited the growth effects of PDGF-BB, an agonist profile consistent with an **A2B** receptor-mediated effect. The **adenosine** receptor antagonists KF17837 and 1,3-dipropyl-8-p-sulfophenylxanthine, but not 8-cyclopentyl-1,3-dipropylxanthine, blocked the growth-inhibitory effects of 2-chloroadenosine and 5'-N-methylcarboxamidoadenosine, an **antagonist** profile consistent with an A2 receptor-mediated effect. Antisense, but not sense or scrambled, oligonucleotides to the **A2B** receptor stimulated basal and PDGF-induced DNA synthesis, cell proliferation, and MAP kinase activity. Moreover, the growth-inhibitory effects of 2-chloroadenosine, 5'-N-methylcarboxamidoadenosine, and erythro-9-(2-hydroxy-3-nonyl) adenine plus iodotubericidin (inhibitors of **adenosine** deaminase and **adenosine** kinase, respectively) were abolished by antisense, but not scrambled or sense, oligonucleotides to the **A2B** receptor. Our findings strongly support the hypothesis that **adenosine** causes inhibition of vascular smooth muscle cell growth by activating **A2B** receptors coupled to inhibition of MAP kinase activity. Pharmacological or molecular biological activation of **A2B** receptors may prevent vascular remodeling associated with hypertension, atherosclerosis, and restenosis following balloon angioplasty.

2000

2/3,AB/12 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12366349 BIOSIS NO.: 200000119851
The novel pyridoxal-5'-phosphate derivative PPNDS potently antagonizes activation of P2X1 receptors.
AUTHOR: Lambrecht Guenter(a); Rettinger Juergen; Baeumert Hans G; Czeche Sittah; Damer Susanne; Ganso Matthias; Hildebrandt Caren; Niebel Beate; Spatz-Kuembel Gerhard; Schmalzing Guenther; Mutschler Ernst
AUTHOR ADDRESS: (a)Department of Pharmacology, Biocentre Niederursel, University of Frankfurt, Marie-Curie-Str. 9, Geb. N260, D-60439, Frankfurt**Germany
JOURNAL: European Journal of Pharmacology 387 (3):pR19-R21 Jan. 17, 2000
ISSN: 0014-2999
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT:
Pyridoxal-5'-phosphate-6-(2'-naphthylazo-6'-nitro-4',8'-disulfonate) (PPNDS) potently antagonized P2X1 receptor-mediated responses in rat vas deferens (pKB = 7.43) and Xenopus laevis oocytes (pIC50 = 7.84). It showed lower (up to 20,000-fold) inhibitory potency on ecto-nucleotidase

in Xenopus oocytes and on P2Y1 receptors in guinea-pig ileum (p A2 = 6.13). PPNDS did not interact with alpha1A-adrenoceptor, **adenosine** A1 and **A2B**, histamine H1 and muscarinic M3 receptors. Thus, PPNDS is a novel, specific P2 receptor **antagonist** and represents the pyridoxal-5'-phosphate derivative with the highest potency at P2X1 receptors.

2000

2/3,AB/128 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12346236 BIOSIS NO.: 200000099738
Adenosine receptor expression and modulation of Ca2+ channels in rat striatal cholinergic interneurons.
AUTHOR: Song Wen-Jie; Tkatch Tatiana; Surmeier D James(a)
AUTHOR ADDRESS: (a)Dept. of Physiology/Northwestern University Institute for Neuroscience, Northwestern University Medical School, 320 E. Superior St., Chicago, IL, 60611**USA
JOURNAL: Journal of Neurophysiology (Bethesda) 83 (1):p322-332 Jan., 2000
ISSN: 0022-3077
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine** is a potent regulator of acetylcholine release in the striatum, yet the mechanisms mediating this regulation are largely undefined. To begin to fill this gap, **adenosine** receptor expression and coupling to voltage-dependent Ca2+ channels were studied in cholinergic interneurons by combined whole cell voltage-clamp recording and single-cell reverse transcription-polymerase chain reaction. Cholinergic interneurons were identified by the presence of choline acetyl-transferase mRNA. Nearly all of these interneurons (90%, n = 28) expressed detectable levels of A1 **adenosine** receptor mRNA. A2a and **A2b** receptor mRNAs were less frequently detected. A3 receptor mRNA was undetectable. **Adenosine** rapidly and reversibly reduced N-type Ca2+ currents in cholinergic interneurons. The A1 receptor **antagonist** 8-cyclopentyl-1,3-dimethylxanthine completely blocked the effect of **adenosine**. The IC50 of the A1 receptor selective agonist 2-chloro-N6-cyclopentyladenosine was 45 nM, whereas it was near 30 mM for the A2a receptor agonist CGS-21680. Dialysis with GDPbetaS or brief exposure to the G protein (Gi/o) alkylating agent N-ethylmaleimide also blocked the **adenosine** modulation. The reduction in N-type currents was partially reversed by depolarizing prepulses. A membrane delimited pathway mediated the modulation, because it was not seen in cell-attached patches when agonist was applied to the bath. Activation of protein kinase C attenuated the **adenosine** modulation. Taken together, our results argue that activation of A1 **adenosine** receptors in cholinergic interneurons reduces N-type Ca2+ currents via a membrane-delimited, Gi/o class G-protein pathway that is regulated by protein kinase C. These observations establish a cellular mechanism by which **adenosine** may serve to reduce acetylcholine release.

2000

2/3,AB/129 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12339318 BIOSIS NO.: 200000092820
Potent antagonists for the human **adenosine A2B** receptor.

Derivatives of the triazolotriazine **adenosine** receptor **antagonist** ZM241385 with high affinity.
AUTHOR: de Zwart Maarten(a); Vollinga Roel C; Beukers Margot W; Sleegers Danielle F; von Frijtag Drabbe Kunzel Jacobien K; de Groote Miriam; IJzerman Ad P
AUTHOR ADDRESS: (a)Division of Medicinal Chemistry, Gorlaeus Laboratories, LACDR, 2300 RA, Leiden**Netherlands
JOURNAL: Drug Development Research 48 (3):p95-103 Nov., 1999
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: A series of novel and known 5-substituted 7-amino-2-(2-furyl)(1,2,4)triazolo(1,5-a)(1,3,5)triazine derivatives were synthesized and tested for **adenosine** receptor antagonism in radioligand binding assays at all four **adenosine** receptor subtypes and for inhibition of the agonist-induced cyclic AMP response at human **A2B** receptors. The known potent **adenosine** A2A receptor **antagonist**, 7-amino-2-(2-furyl)-5-(2-(4-hydroxyphenyl)ethyl)amino(1,2,4)triazolo(1,5-a)(1,3,5)triazine (ZM241385, KiA2A = 1.78 nM) had a Ki value of 16.5 nM at **A2B** receptors in radioligand binding studies on Chinese hamster ovary cells expressing **A2B** receptors. A pA2 value of 7.9 was measured for the inhibition of the cyclic AMP response by **A2B** receptors induced by 5'-N-ethylcarboxamidoadenosine (NECA). In a series of 5-phenyl(alkyl)amino analogs the 5-(2-phenylethyl)amino analog LUF5452 and the 5-benzylamino analog LUF5451 were both more potent than ZM241385 in the cyclic AMP assay at **A2B** receptors. Moreover, Ki values of 9.9 and 7.6 nM were found in binding studies at this receptor subtype, indicating that LUF5451 and LUF5452 are more potent **A2B** receptor antagonists than ZM241385. The affinity of LUF5451 for the A2A receptor (Ki value = 13 nM) showed that the selectivity for this receptor subtype was lost and that a modest **A2B** receptor selectivity was achieved. The 5-(2-phenylhydrazino) derivative LUF5475 showed a high **A2B** receptor affinity (Ki = 7.6 nM), while it was equally active at A2A receptors, being **A2B** receptor-selective with respect to A1 and A3 receptors.

1999

2/3,AB/129 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12231203 BIOSIS NO.: 199900526049
Acyl-hydrazide derivatives of a xanthine carboxylic congener (XCC) as selective antagonists at human **A2B adenosine** receptors.
AUTHOR: Kim Yong-Chul; Karton Yishai; Ji Xiao-duo; Melman Neli; Linden Joel ; Jacobson Kenneth A(a)
AUTHOR ADDRESS: (a)NIDDK, LBC, NIH, Bldg. 8A, Rm. B1A-19, Bethesda, MD, 20892-0810**USA
JOURNAL: Drug Development Research 47 (4):p178-188 Aug., 1999
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The structure-activity relationships (SAR) of 8-phenyl-1,3-dipropylxanthine derivatives in binding to recombinant human **A2B adenosine** receptors were explored, in order to identify selective antagonists. Based on the finding of receptor selectivity in

MPS 1204, containing an N-hydroxysuccinimide ester attached through the p-position of the 8-phenyl substituent (Jacobson et al., 1999): Drug Dev. Res., 47:45-53), a hydrazide and its more stable imide derivatives were synthesized. The hydrazide of XCC (8-(4-((carboxy)methyl)oxy)phenyl)-1,3-dipropylxanthine) was acylated with a variety of mono- and dicarboxylic acids. Ki values were determined in the **adenosine** receptor binding assays. At recombinant human **A2B** receptors expressed in membranes of HEK-293 cells, **antagonist** radioligands used were the xanthine 125I-ABOPX (125I-3-(4-amino-3-iodobenzyl)-8-oxyacetate-1-propyl-xanthine) and the nonxanthine **antagonist** (3H)ZM 241385 ((3H)4-(2-(7-amino-2-(furyl)(1,2,4)triazolo(2,3-a)(1,3,5)triazin-5-ylamino-ethyl)phenol). The initial screening utilized rat A1/A2A receptors and human A3 receptors, and selected compounds were examined at the human A1/A2A subtypes. A 1,2-dimethylmaleimide derivative, 14 (MRS 1595), bound to human **A2B** receptors with a Ki of 19 nM and proved to be selective vs. human A1/A2A/A3 receptors by 160-, 100-, and 35-fold, respectively. Enprofylline (3-propylxanthine) is slightly for **A2B** receptors, suggesting removal of the 1-propyl group; however, combination of the 1-H-3-Pr and 8-phenyl substituents eliminated the selectivity. Other potent and moderately selective **A2B** antagonists were a tetrahydrophthaloyl derivative 18b (MRS 1614, Ki value 10 nM) and amino acid conjugates of the XCC-hydrazide, i.e., the glutarimide 24b (MRS 1626, Ki value 13 nM), and protected dipeptide 27 (MRS 1615, Ki value 11 nM).

1999

2/3,AB/12 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12209646 BIOSIS NO.: 199900504495
Characterization of human **A2B adenosine** receptors: Radioligand binding, Western blotting, and coupling to Gq in human embryonic kidney 293 cells and HMC-1 mast cells.
AUTHOR: Linden Joel(a); Thai Tami; Figler Heidi; Jin Xiaowei; Robeva Anna S
AUTHOR ADDRESS: (a)Departments of Internal Medicine and Molecular Physiology, Health Sciences Center, University of Virginia, Room MR4 6071 Charlottesville, VA**USA
JOURNAL: Molecular Pharmacology 56 (4):p705-713 Oct., 1999
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recombinant human **A2B adenosine** receptors (A2BARs) and receptors extended on the amino terminus with hexahistidine and the FLAG epitope, DYKDDDDK (H/F-**A2B**) were stably over-expressed (to >20,000 fmol/mg protein) in human embryonic kidney 293 cells (HEK-**A2B**). By Western blotting, the H/F-**A2B** receptor runs as a 34.8-kDa glycoprotein. Pharmacological properties of A2BARs were characterized with 125I-3-aminobenzyl-8-phenyl-(4-oxyacetic acid)-1-propylxanthine (KD, 36 nM). In competition binding assays, the affinity of agonists is reduced by substitution on either the N6- or the C-2 position of the adenine ring, whereas 5'-substitutions increase affinity, resulting in the potency order: 5'-N-ethylcarboxamidoadenosine (NECA) much greater than N6-aminobenzyl-NECA approx equal 2-chloroadenosine > 2-(4-(2-carboxyethyl)phenethylamino)-NECA (CGS21680) > N6-aminobenzyladenosine. The A2BAR is potently blocked by the A2A-selective **antagonist** 4-(2-(7-amino-2-(2-furyl)(1,2,4)triazolo-(2,3-a)(1,3,5) triazin-5-yl-amino)ethyl)phenol (ZM241385; Kl, 32 nM for **A2B**, 1.4

nM for A2A) and the A1 selective **antagonist** 8-cyclopentyl-1,3-dipr[redacted]lxanthine (K1, 50.5 nM for **A2B** [redacted].5 nM for A1). The K1 values for the antiasthmatic xanthines, theophylline (7.8 muM) and enprofylline (6.4 muM), are below their therapeutic plasma concentrations (20 to 50 muM), and agree with K1 determinations for inhibition of NECA-stimulated cAMP accumulation in HEK-**A2B** cells. NECA or N6-(2-iodo)benzyl-5'-N-methylcarboxamidodoadenosine (IB-MECA) stimulate inositol trisphosphates and calcium accumulation in HEK-**A2B** or HEK-A3 cells, respectively, but only the A3 response is prevented by pertussis toxin. In human HMC-1 mast cells, A2BAR activation stimulates calcium mobilization and cAMP accumulation. We conclude that HEK-**A2B** cells and HMC-1 mast cells possess A2BAR glycoproteins that are coupled to both Gq/11 and Gs.

1999

2/3,AB/127 (Item 32 from file: 5)
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12208243 BIOSIS NO.: 199900503092
Selective A3 **adenosine** receptor antagonists: Water-soluble 3,5-diacyl-1,2,4-trialkylpyridinium salts and their oxidative generation from dihydropyridine precursors.
AUTHOR: Xie Rongyuan; Li An-Hu; Ji Xiao-Duo; Melman Neli; Olah Mark E; Stiles Gary L; Jacobson Kenneth A(a)
AUTHOR ADDRESS: (a)Molecular Recognition Section, LBC, NIDDK, NIH, Bldg. 8A, Rm. B1A-19, Bethesda, MD, 20892-0810**USA
JOURNAL: Journal of Medicinal Chemistry 42 (20):p4232-4238 Oct. 7, 1999
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LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: A3 **adenosine** receptor antagonists are sought for their potential antiinflammatory, antiasthmatic, and antiischemic properties. We have found that 3,5-diacyl-1,2,4-trialkyl-6-phenyl-pyridinium derivatives constitute a novel class of selective A3 **adenosine** receptor antagonists. The structure-activity relationships of this class of antagonists, incorporating the 3-thioester, have been explored. The most potent analogue in this group was 2,4-diethyl-1-methyl-3-(ethylsulfanylcarbonyl)-5-ethyloxycarbonyl-6-phenylpyridinium iodide (11), which had an equilibrium inhibition constant (Ki) value of 219 nM at human A3 receptors (binding of (125I)-AB-MECA (N6-(4-amino-3-iodobenzyl)-5'-N-methylcarbamoyladenosine)) expressed in Chinese hamster ovary (CHO) cells and >10 muM at rat brain A1 and A2A receptors and at recombinant human **A2B** receptors. Compound 11 could be generated through oxidation of the corresponding 3,5-diacyl-1,2,4-trialkyl-6-phenyl-1,4-dihydropyridine, 24, with iodine or in the presence of rat brain homogenates. A 6-cyclopentyl analogue was shown to increase affinity at human A3 receptors upon oxidation from the 1-methyl-1,4-dihydropyridine analogue, 25, to the corresponding pyridinium derivative, 23 (Ki 695 nM), suggesting a prodrug scheme. Homologation of the N-methylpyridinium derivatives to N-ethyl and N-propyl at the 1-position caused a progressive reduction in the affinity at A3 receptors. Modifications of the alkyl groups at the 2-, 3-, 4-, and 5-positions failed to improve potency in binding at A3 receptors. The pyridinium antagonists are not as potent as other recently reported, selective A3 receptor antagonists; however, they display uniquely high water solubility (43 mM for 11). Compound 11 antagonized the inhibition of adenylate cyclase elicited by IB-MECA in CHO cells expressing the human A3 **adenosine** receptor, with a KB value of 399 nM, and did not act as an agonist, demonstrating that the pyridinium salts are pure

antagonists.

1999

2/3,AB/128 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12203209 BIOSIS NO.: 199900498058
Adenosine receptor activation induces vascular endothelial growth factor in human retinal endothelial cells.
AUTHOR: Grant Maria B(a); Tarnuzzer Roy W; Caballero Sergio; Ozeck Mark J; Davis Margaret I; Spoerri Polyxenie E; Feoktistov Igor; Biaggioni Italo; Shryock John C; Belardinelli Luiz
AUTHOR ADDRESS: (a)Department of Medicine, Division of Endocrinology and Metabolism, University of Florida, Gainesville, FL, 32610-0226**USA
JOURNAL: Circulation Research 85 (8):p699-706 Oct. 15, 1999
ISSN: 0009-7330
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Adenosine**, released in increased amounts by hypoxic tissues, is thought to be an angiogenic factor that links altered cellular metabolism caused by oxygen deprivation to compensatory angiogenesis. **Adenosine** interacts with 4 subtypes of G protein-coupled receptors, termed A1, A2A, **A2B**, and A3. We investigated whether **adenosine** causes proliferation of human retinal endothelial cells (HRECs) and synthesis of vascular endothelial growth factor (VEGF) and, if so, which **adenosine** receptor subtype mediates these effects. The nonselective **adenosine** receptor agonist 5'-N-ethylcarboxamidoadenosine (NECA), in a concentration-dependent manner, increased both VEGF mRNA and protein expression by HRECs, as well as proliferation. This proliferative effect of NECA was inhibited by the addition of anti-human VEGF antibody. NECA also increased insulin-like growth factor-I and basic fibroblast growth factor mRNA expression in a time-dependent manner and cAMP accumulation in these cells. In contrast, neither the A1 agonist N6-cyclopentyladenosine nor the A2A agonist 2-p-(2-carboxyethyl) phenethylamino-NECA caused any of the above effects of NECA. The effects of NECA were not significantly attenuated by either the A2A **antagonist** SCH58261 or the A1 **antagonist** 8-cyclopenthyl-1,3-dipropylxanthine. However, the nonselective **adenosine** receptor **antagonist** xanthine amine congener completely inhibited the effects of NECA. Addition of antisense oligonucleotide complementary to **A2B adenosine** receptor mRNA inhibited VEGF protein production by HRECs after NECA stimulation. Thus, the **A2B adenosine** receptor subtype appears to mediate the actions of **adenosine** to increase growth factor production, cAMP content, and cell proliferation of HRECs. **Adenosine** activates the **A2B adenosine** receptor in HRECs, which may lead to neovascularization by a mechanism involving increased angiogenic growth factor expression.

1999

2/3,AB/129 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12003068 BIOSIS NO.: 199900283587
Studies on ocular pharmacology (Rept. 29) Role of **adenosine** receptors in regulation of intraocular pressure in albino rabbits.

AUTHOR: Watanabe Aki(a); Yosokawa Tomokazu(a); Misawa Miwa(a)
AUTHOR ADDRESS: (a)Dept. [redacted] Pharmacol., School of Pharma[redacted] Hoshi Univ., Tokyo, 142-8501**Japan
JOURNAL: Japanese Journal of Pharmacology 79 (SUPPL. 1):p127P 1999
CONFERENCE/MEETING: 72nd Annual Meeting of the Japanese Pharmacological Society Sapporo, Japan March 22-25, 1999
SPONSOR: Japanese Pharmacological Society
ISSN: 0021-5198
RECORD TYPE: Citation
LANGUAGE: English
1999

2/3,AB/130 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11929595 BIOSIS NO.: 199900175704
Adenosine A2B receptors as therapeutic targets.
AUTHOR: Feoktistov Igor; Wells Jack N; Biaggioni Italo(a)
AUTHOR ADDRESS: (a)Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN, 37232-2195**USA
JOURNAL: Drug Development Research 45 (3-4):p198-206 Nov.-Dec., 1998
ISSN: 0272-4391
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent evidence indicates that **A2B** receptors mediate cellular functions with potential clinical relevance. Both A2A and **A2B** receptors mediate vasodilation, and the receptor type involved depends on the vascular bed and species studied. In some experimental models, **A2B**-induced vasodilation is mediated by the endothelium, but it is unclear whether this vasodilation is due to nitric oxide or whether **A2B** receptors also mediate direct vascular smooth muscle relaxation. **A2B** receptors expressed in smooth muscle cells inhibit their growth, raising the possibility that these receptors play a role in the vascular remodeling process observed in hypertension and atherosclerosis. **A2B** receptors are also expressed in neurons, and there are several examples of these receptors mediating neuroexcitatory actions, including potentiation of neurotransmitter release. The highest expression of **A2B** receptors is found throughout the intestinal tract. During diarrheal processes, neutrophils recruited into intestinal crypts release a soluble "neutrophil-derived secretagogue," which then increases intestinal secretion. It is now known that this neutrophil product is AMP, which is then converted to **adenosine** to activate **A2B** receptors expressed in intestinal epithelium. It was also recently found that activation of human mast cells by **adenosine** is mediated by **A2B** receptors. Mast cell activation is involved in **adenosine**-induced bronchoconstriction in asthmatics, suggesting that **A2B** receptors are involved in this process. Our understanding of the functional role of **A2B** receptors is hindered by the lack of selective agonist and **antagonist** of this receptor type. Recent studies suggest the feasibility of developing **A2B** antagonists. Such agents may prove useful in the treatment of diarrheal diseases and in asthma.

1998

2/3,AB/131 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11874502 BIOSIS NO.: 199900120611

Comparison of CGS 15943, ZM 241385 and SCH 58261 as antagonists at human **adenosine** receptors.
AUTHOR: Ongini Ennio(a); Dionisotti Silvio; Gessi Stefania; Irenius Eva; Fredholm Bertil B
AUTHOR ADDRESS: (a)Schering-Plough Res. Inst., San Raffaele Science Park, Via Olgettina 58, I-20132 Milan**Italy
JOURNAL: Naunyn-Schmiedeberg's Archives of Pharmacology 359 (1):p7-10 Jan., 1999
ISSN: 0028-1298
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Three structurally related non-xanthine compounds, CGS 15943, ZM 241385 and SCH 58261, are potent A2A **adenosine** receptor antagonists and have been used as tools in many pharmacological studies. We have now characterized their affinity and selectivity profile on human **adenosine** receptors stably transfected into either CHO cells (A1 and **A2B** receptors) or HEK-293 cells (A2A and A3 receptors). In binding studies using (3H)SCH 58261 as a radioligand, the three compounds were equally potent at A2A receptors, their Ki value being less than 1 nM. Affinity for A1 and A3 receptors was measured using (3H)DPCPX and (125I)AB-MECA as radioligands. Given the lack of selective ligands, interaction with **A2B** receptors was assessed using the cAMP accumulation assay following stimulation by the **adenosine** receptor agonist N-ethylcarboxamidoadenosine (NECA). CGS 15943 was almost as potent at A1 receptors (Ki 3.5 nM) as at A2A receptors, showed moderate affinity for A3 receptors (Ki 95 nM) and also interacted with **A2B** receptors (Ki 44 nM; pA2 7.5). ZM 241385 showed little affinity for A1 receptors (Ki 255 nM), and did not interact with A3 receptors (Ki>10 muM); however, it displayed moderate affinity for **A2B** receptors (Ki 50 nM; pA2 7.3). SCH 58261 had weak affinity for A1 receptors (Ki 287 nM), no interaction with A3 receptors (Ki>10 muM), and showed negligible interaction with **A2B** receptors (Ki 5 muM; pA2 6.0). These data indicate that SCH 58261 is the most selective A2A **antagonist** currently available. Moreover, the different receptor selectivity of these three chemically related compounds provides useful information to progress with structure-activity relationship studies.

1999

2/3,AB/13 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11836700 BIOSIS NO.: 199900082809
Potentiation by **adenosine** of histamine-induced bronchospasm in anaesthetized guinea-pig: Receptor subtype/s involved.
AUTHOR: Breschi Maria Cristina(a); Nieri Paola; Lazzeri Nicola; Macchia Marco
AUTHOR ADDRESS: (a)Dipartimento Psichiatria Neurobiologia Farmacologia Biotecnologie, Via Bonanno n 6, 56126 Pisa**Italy
JOURNAL: Drug Development Research 45 (1):p17-22 Sept., 1998
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A potentiating effect by **adenosine** on the bronchoconstrictile response to histamine has been previously described in a guinea-pig model (Breschi et al. (1994) Pharmacology 49:42-51). In the present study, the subtype(s) of purinergic receptors involved in this modulatory effect of the nucleoside have been investigated. A possible role for P2 receptors or for the putative P3 receptor subtype was

excluded because of the very poor modulatory effect of the P2 agonist alpha,beta-methylene A[redacted] when compared with the effects of all the P1 agonists tested, with the exception of 5'-N-Methyl-N6-(3-iodobenzyl) **adenosine**. The order of potency revealed for the P1 agonists was R-N6-(2-phenylisopropyl)**adenosine** (R-PIA) = 5'-N-methylcarboxamidoadenosine > N6-2-(4-aminophenyl)ethyladenosine gtoreq **adenosine** and in the presence of R-PIA, a significantly greater maximal effect was observed. Among the **adenosine** receptor antagonists evaluated, the A2 **antagonist** 3,7-dimethyl-1-propargylxanthine even increased the effect of **adenosine** and no influence was evident with the reported **A2B antagonist** enprofylline. A significant reduction of the potentiating activity of **adenosine** was, on the contrary, obtained with the nonselective blocker theophylline or the A1 **antagonist** DPCPX. In conclusion, the above data suggest that the potentiation of histamine-induced bronchoconstriction by **adenosine** is mediated by the stimulation of A1 receptors.

1998

2/3,AB/138 (Item 38 from file: 5)
DIALOG File 5:Biosis Previews(R)
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11626068 BIOSIS NO.: 199800408404
Further pharmacological characterization of the **adenosine** receptor subtype mediating inhibition of oxidative burst in human isolated neutrophils.
AUTHOR: Harmon J P; Bray-French K M; Phillips R M; Fozard J R(a)
AUTHOR ADDRESS: (a)Novartis Pharma Ltd., S.386.510, CH-4002, Basel** Switzerland
JOURNAL: Drug Development Research 43 (4):p214-224 April, 1998
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The aims of this study were to characterize the **adenosine** receptor subtype mediating inhibition of superoxide anion generation induced by N-formyl-methionyl-leucylphenylalanine (fMLP) in human neutrophils and to test the hypothesis that **adenosine** 3':5'-cyclic monophosphate (cAMP) is the second messenger mediating such inhibition. Superoxide anion generation induced by a submaximal concentration of fMLP (1 muM) was inhibited in a concentration-dependent manner by **adenosine** receptor agonists with a rank order of potency of N-ethylcarboxamidoadenosine (NECA) > 2(4-(2-carboxyethyl)phenyllethylamino)-5'-N-ethylcarboxamido **adenosine** (CGS 21680) > (R)-N6-phenyl-2-propyladenosine ((R)-PIA) > 2-Chloro-N6-(3-iodobenzyl)9-(5-methylcarbamoyl)-beta-D-ribofuranosyl) adenine (2-Cl-IB-MECA) > N6-cyclopentyladenosine (CPA) > (S)-N6-phenyl-2-propyladenosine ((S)-PIA) > N6-(4-amino-3-iodobenzyl) **adenosine**-9'-N-methyl-uronamide (AB-MECA); this order of potency is consistent with the activation of A2A **adenosine** receptors. The nonselective A1, A2A, and **A2B** receptor **antagonist** 8-p- sulphophenyl) theophylline (8-SPT; 10 muM) produced blockade of each of the agonists (PKB values 4.79-5.68). The selective A1 **adenosine** receptor **antagonist** 1,3-dipropyl-8-cyclopentylxanthine (DPCPX; 100 nM) and the selective A3 **adenosine** receptor **antagonist** 3-(3 iodo-4-aminobenzyl)-8-(4-oxyacetate)phenyl-1-propylxanthine (I-ABOPX; 200 nM) also produced blockade of all the agonists (PKB values 7.37-7.61 and 6.75-7.52, respectively); however, the concentrations required were higher than those which are considered selective for the A1 or A3 receptors. The selective A2A receptor **antagonist**, 4-(2-(7-amino-2-(2-furyl) (1,2,4) triazolo (2,3-a) (1,3,5) triazin-5-yl

amin(ethyl) phenol (ZM 241385; 100 nM), powerfully suppressed the inhibition of the oxid[redacted]ve burst induced by each of th[redacted]gonists. A Schild analysis of the effects of ZM 241385, 1-100 nM, against NECA and CGS 21680 was carried out. ZM 241385 produced concentration-dependent, parallel shifts of the concentration-effect curves to both NECA and CGS 21680, with pA2 values of 9.62 and 9.59, respectively. Together, these data establish that inhibition of the oxidative burst in human isolated neutrophils, induced by **adenosine** receptor agonists, is mediated by the A2A receptor. NECA (0.01-10 muM) induced a concentration-dependent increase in the intracellular cAMP content of neutrophils. This effect was inhibited in a dose-dependent manner by ZM 241385 (0.001-10 muM), consistent with activation of A2A **adenosine** receptors. The results clearly demonstrate that in human neutrophils inhibition of the fMLP-induced oxidative burst by **adenosine** receptor agonists is mediated via activation of A2A **adenosine** receptors linked positively to cAMP. No evidence of A1, **A2B**, or A3 **adenosine** receptor-mediated modulation of oxidative burst was found.

1998

2:3,AB:134 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11436171 BIOSIS NO.: 199800217503
SCH 58261: A selective A(2)A **adenosine** receptor **antagonist**.
AUTHOR: Ongini Ennio(a)
AUTHOR ADDRESS: (a)Schering-Plough Res. Inst., San Raffaele Science Park, Via Olgettina 58, I-2132 Milano, MI**Italy
JOURNAL: Drug Development Research 42 (2):p63-70 Oct., 1997
ISSN: 0272-4391
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The recent discovery of selective antagonists for the A2A **adenosine** receptors has been of great help to further research in this field. One compound, SCH 58261, 5-amino-7-(beta-phenylethyl)-2-(8-furyl)pyrazolo(4,3-e)-1,2,4-triazolo(1,5-c)pyrimidine, is playing a key part in a variety of studies. This review describes its pharmacological characteristics as they are emerging in various laboratories. The compound has an affinity in the low nM range (Ki value of 1-2 nM) for A2A receptors located on membranes from a variety of tissues and cell types, including rat and bovine brain striatum, human platelets, lymphocytes and neutrophils, porcine coronary arteries, and CHO cells transfected with the cloned human A2A receptors. SCH 58261 has little or no affinity up to the muM range for **adenosine A2B**, A3, or other G protein-coupled receptors. Selectivity for A2A vs. A1 receptors varies from 53- to 750-fold, depending on membranes or type of assay. SCH 58261 blocks A2A-receptor mediated increase of cyclic AMP formation with high potency (e.g., IC50 values between 15 and 20 nM in human white blood cells). The tritiated form of SCH 58261 specifically labels A2A receptors in discrete regions of the rat brain such as caudate-putamen, nucleus accumbens, and tuberculum olfactorium. In classic in vitro bioassays, such as A2A-receptor-mediated vasodilation in coronary arteries, SCH 58261 displays competitive antagonistic properties (e.g., pA2 value of 9.5 in porcine coronary arteries). In assays involving responses mediated by A1 or **A2B** receptors, SCH 58261 shows little or no activity up to concentrations about 100-fold higher than those affecting A2A receptors (higher concentrations not being testable due to its poor water solubility). In the rat, SCH 58261 enhances locomotor activity (at 3.7 mg/kg ip), increases wakefulness (10 mg/kg ip) and slightly increases both blood pressure and heart rate (10 mg/kg ip). These activities appear

to be specifically mediated by A2A receptors since the drug counteracts the effect of A2A receptor agonists in some experimental paradigms. In models mimicking CNS disorders, SCH 58261 potentiates the activity of L-DOPA or dopamine receptor agonists in the 6-hydroxydopamine-lesioned rat model. Moreover, the compound reduces brain infarct size in a rat model of cerebral ischemia. Altogether, SCH 58261 and its radiolabeled form have emerged as interesting tools for better understanding the function of A2A receptors in physiological or altered conditions. Moreover, the neuroprotective properties of SCH 58261 indicate that drugs of this class have a potential for treatment of brain damage produced by Parkinson's disease or stroke.

1997

2/3,AB/135 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11403510 BIOSIS NO.: 199800184842
The A[2]A **adenosine** receptor mediates coronary vasodilation.
AUTHOR: Belardinelli Luiz(a); Shryock John C; Snowdy Stephen; Zhang Yi; Monopoli Angela; Lozza Gianluca; Ongini Ennio; Olsson Ray A; Dennis Donn M
AUTHOR ADDRESS: (a)Univ. Florida, P.O. Box 100277, Gainesville, FL 32610-0277**USA
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 284 (3):p 1064-1073 March, 1998
ISSN: 0022-3565
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The coronary vasodilation caused by **adenosine** is due to activation of A2 **adenosine** receptors (A2AdoRs), but the subtype or subtypes of A2AdoR (A2A and/or **A2B**) that mediate this action are uncertain. The purpose of this study was to test the hypothesis that A2AAdoRs mediate coronary vasodilation caused by exogenous or endogenous **adenosine** in the guinea pig isolated perfused heart. The newly described A2AAdoR **antagonist** SCH58261 was used to selectively block A2AAdoRs. Attenuations by SCH58261 of increases in coronary conductance (A2 response) and of atrioventricular nodal conduction time (A1 response) caused by exogenous and endogenous **adenosine** and by agonists with relative selectivity for A2A and A1AdoRs were measured. The CGS21680-induced increase of coronary conductance was antagonized by SCH58261 in a concentration-dependent and competitive manner with a KB value of 9.01 nm. Also reversed by SCH58261 (60 nmol/L) were the increases in coronary conductance caused by the relatively selective A1Ao R agonists CCPA (70 nM), and (R)-(-)Nb-(2-phenyl-isopropyl) **adenosine** (60 nM) but not those caused by sodium nitroprusside (1.2 muM) and diltiazem (0.4 muM). SCH58261 (ltoreq100 nM) did not attenuate the A1AdoR-mediated prolongations of S-H interval caused by either **adenosine** or CCPA. SCH58261 attenuated the coronary vasodilation caused by 50 nM **adenosine** with an IC50 value of 6.8 +- 0.6 nM. The coronary vasodilations caused by the nucleoside uptake inhibitor draflazine and the **adenosine** kinase inhibitor iodotubercidin were completely reversed by 60 nM SCH58261 or **adenosine** deaminase (7 U/ml). Thus, the A2AAdoR plays a major role as mediator of coronary vasodilation caused by exogenous and endogenous **adenosine** and by AdoR agonists.

1998

2/3,AB/136 (Item 41 from file: 5)

DIALOG(P)File 5:Biosis Previews(R)
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11220759 BIOSIS NO.: 199800002091
A|1 **adenosine** receptors potently regulate heart rate in mammalian embryos.
AUTHOR: Hofman Paul L; Hiatt Kelly; Yoder Mervin C; Rivkees Scott A(a)
AUTHOR ADDRESS: (a)Section Pediatric Endocrinol., Yale Univ. Sch. Med., PO Box 208081, 464 Congress St., New Haven,**USA
JOURNAL: American Journal of Physiology 273 (4 PART 2):pR1374-R1380 Oct., 1997
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A1 **adenosine** receptors (A1ARs) have been recently shown to be expressed in rodent embryonic hearts at very early stages of development. To determine the functional significance of fetal cardiac A1AR expression during embryogenesis, murine fetal heart preparations were studied between postconceptual days 9 and 12. Dose-response curves generated using a variety of **adenosine** agonists revealed that A1AR activation potently regulated fetal heart rates. The A1AR agonist, N6-cyclopentyladenosine, inhibited heart rates in a dose-dependent manner (half-maximal effective concentration = 3.6 X 10-8 M) and stopped fetal cardiac contractions in 63% of preparations. In contrast, A2a and **A2b** receptor activation did not alter heart rates, and activation of A3 receptors produced modest declines in heart rates. Endogenous **adenosine** also acted tonically to suppress fetal heart rates, as demonstrated by the A,AR **antagonist** 1,3-dipropyl-8cyclopentylxanthine, increasing heart rates, whereas the **adenosine** reuptake blocker dipyridamole lowered fetal heart rates. Pertussis toxin treatment blocked A1AR action, showing that A1AR action was G protein mediated. Using drugs that alter cAMP levels and ion channel action, we were able to show that A1AR action involves events mediated by cAMP, ATP-dependent K, L-type calcium, sodium, and chloride channels, and the pacemaker current. These data show that **adenosine** and A1ARs potently regulate mammalian heart rates via multiple effector systems at very early stages of prenatal development.

1997

2/3,AB/137 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08288088 BIOSIS NO.: 000094059386
RELATIVE AGONIST POTENCIES OF C-2-SUBSTITUTED ANALOGUES OF **ADENOSINE** EVIDENCE FOR **ADENOSINE** A-2B RECEPTORS IN THE GUINEA-PIG AORTA
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AUTHOR ADDRESS: DEP. PHARMACOL., WHITBY RES. INC., 2801 RESERVE ST., RICHMOND, VA. 23220, USA.
JOURNAL: EUR J PHARMACOL 216 (2). 1992. 235-242. 1992
FULL JOURNAL NAME: European Journal of Pharmacology
CODEN: EJPHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Nine C2-substituted **adenosine** analogues that are potent and selective for the A2-**adenosine** receptor were tested for their ability to induce relaxations of the guinea pig aorta. Compounds tested were 2-phenylethoxyadenosine (PEA), 2-phenylethoxy-5'-N-ethylcarboxamidoadenosine (PENECA), 2-cyclohexylethoxyadenosine (CEA), 2-fluorophenylethoxyadenosine (FPEA),

2-methoxyphenylethoxyadenosine (MPEA), 2-naphthylethoxyadenosine (NEA), 2-phenylaminoadenosine (CV-1808), 2-phenylethylaminoadenosine (PEAA) and 2-carboxyethylphenethylamino-5'-ethylcarboxamidoadenosine (CGS21680). The responses to these agents were compared to those of three standard **adenosine** receptor agonists, 5'-N-ethylcarboxamidoadenosine (NECA), N6-cyclohexyladenosine (CHA) and R-N6-phenylisopropyladenosine (R-PIA). The C2-ethoxyadenosine analogues were 30- to 140-fold less potent than NECA and the C2-amino-substituted analogues were 250 to 1000-fold less potent than NECA at inducing relaxations of the guinea pig aorta. All of the analogues were also less potent than the A1-selective agonist R-PIA. However, only responses to NECA were competitively antagonized by the non-selective **adenosine** receptor **antagonist** 8-phenyltheophylline (8-PT), pKB = 6.83 .+-. 0.05. The results suggest that the C2-substituted analogues produce relaxations of the guinea pig aorta through a combination of actions at A2-**adenosine** receptors and at xanthine resistant sites. The lack of potency of these analogues at activating the xanthine sensitive A2-receptors in the guinea pig aorta suggests that these **adenosine** receptors may be of the **A2b** -subtype.

1992

2/3,AB/138 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08184092 BIOSIS NO.: 000094007865
CHARACTERIZATION OF P-1-PURINOCEPTORS ON RAT DUODENUM AND URINARY BLADDER
AUTHOR: NICHOLLS J; HOURANI S M O; KITCHEN I
AUTHOR ADDRESS: RECEPTORS CELLULAR REGULATION RESEARCH GROUP, SCH. BIOL. SCI., UNIV. SURREY, GUILDFORD, SURREY GU2 5XH.
JOURNAL: BR J PHARMACOL 105 (3). 1992. 639-642. 1992
FULL JOURNAL NAME: British Journal of Pharmacology
CODEN: BJPCB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: 1 The P1-purinoceptors mediating relaxation of the rat duodenum and inhibition of contraction of the rat urinary bladder were characterized by use of **adenosine** and its analogues 5'-N-ethylcarboxamidoadenosine (NECA), N6-cyclopentyladenosine (CPA) and 2-p- (carboxyethyl)phenethylamino)-5'-carboxamidoadenosine (CGS 21680), as well as the A1-selective **antagonist** 1,3-dipropyl-8-cyclo-pentylxanthine (DPCPX). The stable analogue of **adenosine** 5'-triphosphate (ATP), adenylyl 5'-(.beta.,.gamma.-methylene) diphosphonate (AMPPCP), was also used as previous work had indicated that it has a direct action on some P1 receptors in addition to its P2-purinoceptor activity. 2 In the rat duodenum, the order of potency of the **adenosine** agonists was NECA .gtoreq. CPA > AMPPCP = **adenosine** > CGS 21680, and DPCPX antagonized CPA and AMPPCP at a concentration of 1 nM whereas equivalent antagonism of NECA and **adenosine** required a concentration of 1 .mu.M. This suggests the presence of a mixture of A1 and A2 receptors in this tissue, with CPA and AMPPCP acting on the A1 and NECA and **adenosine** acting on the A2 receptors. 3 In the rat bladder, the order of potency of the **adenosine** agonists for inhibition of carbachol-induced contractions was NEC .mchgt. **adenosine** > CPA = CGS 215680, and a concentration of DPCPX of 1 .mu.M was required to antagonize responses to NECA and **adenosine**. This suggests the presence of A2 receptors in this tissue. ATP and AMPPCP each caused contractions which were not enhanced by DPCPX (1 .mu.M) which suggests that in this tissue AMPPCP was acting only via P2 receptors and had no P1 agonist activity. That AMPPCP was active on the A1 receptors in the duodenum but inactive on the A2 receptors in the bladder implies that it

has selectivity for the A1 subtype. 4 That CGS 21680, which has been reported to bind selectively to the high affinity A2a subclass of A2 receptors, had a very low potency on the A2 receptors in the duodenum and in the bladder suggests that these receptors are of the low affinity **A2b** subclass.

1992

2/3,AB/139 (Item 44 from file: 5)
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07502359 BIOSIS NO.: 000091076228
CHARACTERIZATION OF THE BINDING OF A NOVEL NONXANTHINE **ADENOSINE** **ANTAGONIST** RADIOLIGAND TRITIATED CGS-15943 TO MULTIPLE AFFINITY STATES OF THE **ADENOSINE** A-1 RECEPTOR IN THE RAT CORTEX
AUTHOR: JARVIS M F; WILLIAMS M; DO U H; SILLS M A
AUTHOR ADDRESS: RHONE-POULENC RORER CENTRAL RES., 680 ALLENDALE ROAD, KING OF PRUSSIA, PA. 19406.
JOURNAL: MOL PHARMACOL 39 (1). 1991. 49-54. 1991
FULL JOURNAL NAME: Molecular Pharmacology
CODEN: MOPMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The triazoloquinazoline CGS 15943 is the first reported nonxanthine **adenosine antagonist** that has high affinity for brain **adenosine** receptors. In the present study, the binding of [3H]CGS 15943 to recognition sites in rat cortical membranes was characterized. Saturation experiments revealed that [3H]CGS 15943 labeled a single class of recognition sites with high affinity (Kd = 4 nM) and limited capacity (Bmax = 1.5 pmol/mg of protein). Competition studies revealed that the binding of [3H]CGS 15943 was consistent with the labeling of brain **adenosine** A1 receptors. **Adenosine** agonists inhibited 1 nM [3H] CGS 15943 binding with the following order of activity N6-cyclopentyladenosine (IC50 = 15 nM) > 2-chloroadenosine > (R)-N6-phenylisopropyladenosine > 5'-N6-ethylcarboxamidoadenosine > (S)N6-phenylisopropyladenosine > CGS 21680 .dag. CV 1808 (IC50 > 10,000 nM). The potency order for **adenosine** antagonists was CGS 15943 (IC50 = 5 nM) > 8-phenyltheophylline > 1,3-dipropyl-8-(4-amino-2-chloro)phenylxanthine > 1,3-diethyl-8-phenylxanthine > theophylline = caffeine (IC50 > 10,000 nM). **Antagonist** inhibition curves were steep and best described by a one-site binding model. In contrast, **adenosine** A1 agonist competition curves were shallow, as indicated by Hill coefficients less than unity. Computer analysis revealed that these inhibition curves were best described by a two-site binding model. Agonist competition curves generated in the presence of 1 mM GTP resulted in a rightward shift and steepening of the inhibition-concentration curves, whereas **antagonist** binding was not altered in the presence of GTP. The complex binding interactions found with **adenosine** agonists indicate that [3H]CGS 15943 labels both high and low affinity components of the **adenosine** A1 receptor in the rat cortex. Additionally, the present data also provide some evidence that [3H]CGS 15943 may also recognize an additional low affinity binding component, which may represent a putative low affinity **A2b** receptor in this tissue.

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13510788 BIOSIS NO.: 200200139609
Blockade of in vivo VEGF-mediated angiogenesis by antisense gene **therapy**: Role of Flk-1 and Flt-1 receptors.
AUTHOR: Marchand Genevieve S; Noiseux Nicolas; Tanguay Jean-Francois; Sirois Martin G(a)
AUTHOR ADDRESS: (a)Montreal Heart Institute, 5000 Belanger St., Montreal, Quebec, H1T 1C8**Canada E-Mail: mgsirois@icm.umontreal.ca
JOURNAL: American Journal of Physiology 282 (1 Part 2):pH194-H204 January, **2002**
MEDIUM: print
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Angiogenesis, the formation of new blood vessels from preexisting ones, is a critical component of various pathologies such as tumor progression, rheumatoid arthritis, and **retinopathies**. Vascular **endothelial** growth factor (VEGF) is a mitogenic and chimiotactic factor capable of inducing angiogenesis through the activation of its receptors, fetal liver kinase-1 (Flk-1) and fms-like tyrosine kinase-1 (Flt-1), expressed on **endothelial cells**. The purpose of the present study was to assess if a treatment with antisense (AS) oligonucleotides directed against VEGF receptors Flk-1 or Flt-1 mRNA could prevent VEGF-mediated angiogenesis. With the use of miniosmotic pumps, phosphate-buffered saline, VEGF, or VEGF combined with AS-Flk-1, AS-Flt-1, or AS-scrambled oligonucleotides were released in mouse testis for 14 days. VEGF (1, 2.5, and 5 mug) increased the formation of new capillary blood vessels by 236, 246, and 287%, respectively. The combination of AS-Flk-1 or AS-Flt-1 (200 mug) to VEGF (2.5 mug) reduced by 87 and 85% the formation of new blood vessels, respectively, and the expression of their corresponding proteins. These data demonstrate the **therapeutical** potential of AS-Flk-1 or AS-Flt-1 to prevent VEGF-mediated angiogenesis in vivo.

2002

5/3,AB/59 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13397761 BIOSIS NO.: 200200026582
A potential use of a synthetic **retinoid** TAC-101 as an orally active agent that blocks angiogenesis in liver metastases of human stomach cancer **cells**.
AUTHOR: Tsutomu Oikawa(a); Koji Murakami; Masaki Sano; Jiro Shibata; Konstanty Wierzba; Yuji Yamada
AUTHOR ADDRESS: (a)Pharmaceutical Research and Development Center, Tokyo Metropolitan Institute of Medical Science (Rinshoken), Tokyo Metropolitan Organization for Medical Research, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, 113-8613**Japan E-Mail: oikawa@rinshoken.or.jp
JOURNAL: Japanese Journal of Cancer Research 92 (11):p1225-1234 November, **2001**
MEDIUM: print
ISSN: 0910-5050
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: TAC-101 (4-(3,5-bis(trimethylsilyl)benzamido)benzoic acid) is a novel, synthetic **retinoid** that is effective against liver

without exerting a direct antiangiogenic activity.

5/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11277877 21316594 PMID: 11424092
Pigment epithelium-derived factor inhibits **retinal** and choroidal neovascularization.
Mori K; Duh E; Gehlbach P; Ando A; Takahashi K; Pearlman J; Mori K; Yang H S; Zack D J; Ettyreddy D; Brough D E; Wei L L; Campochiaro P A
The Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
Journal of cellular physiology (United States) Aug **2001**, 188 (2) p253-63, ISSN 0021-9541 Journal Code: 0050222
Contract/Grant No.: EY05951; EY; NEI; EY12609; EY; NEI; P30EY1765; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In this study, we investigated whether overexpression of pigment epithelium-derived factor (PEDF) by gene transfer can inhibit neovascularization by testing its effect in three different **models** of ocular neovascularization. Intravitreous injection of an adenoviral vector encoding PEDF resulted in expression of PEDF mRNA in the eye measured by RT-PCR and increased immunohistochemical staining for PEDF protein throughout the **retina**. In mice with laser-induced rupture of Bruch's membrane, choroidal neovascularization was significantly reduced after intravitreous injection of PEDF vector compared to injection of null vector or no injection. Subretinal injection of the PEDF vector resulted in prominent staining for PEDF in **retinal** pigmented epithelial **cells** and strong inhibition of choroidal neovascularization. In two **models** of **retinal** neovascularization (transgenic mice with increased expression of vascular **endothelial** growth factor (VEGF) in photoreceptors and mice with oxygen-induced ischemic **retinopathy**), intravitreous injection of null vector resulted in decreased neovascularization compared to no injection, but intravitreous injection of PEDF vector resulted in further inhibition of neovascularization that was statistically significant. These data suggest that sustained increased intraocular expression of PEDF by gene **therapy** might provide a promising approach for treatment of ocular neovascularization. Copyright 2001 Wiley-Liss, Inc.

5/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11249393 21282634 PMID: 11389035
Angiogenesis in acute promyelocytic leukemia: induction by vascular **endothelial** growth factor and inhibition by all-trans **retinoic** acid.
Kini A R; Peterson L A; Tallman M S; Lingen M W
Department of Pathology, Northwestern University Medical School, Chicago, IL, USA.
Blood (United States) Jun 15 **2001**, 97 (12) p3919-24, ISSN 0006-4971 Journal Code: 7603509
Contract/Grant No.: P20 CA79403; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent studies indicate that angiogenesis is important in the pathogenesis of leukemias, apart from its well-established role in solid

tumors. In this study, the possible role of angiogenesis in acute promyelocytic leukemia (APL) was explored. Bone marrow trephine biopsies from patients with APL showed significantly increased microvessel density and hot spot density compared with normal control bone marrow biopsies. To identify the mediators of angiogenesis in APL, quantitative and functional assays were performed using the NB4 APL **cell** line as a **model** system. Conditioned media (CM) from the NB4 **cells** strongly stimulated **endothelial cell** migration. CM from the NB4 **cells** contained high levels of vascular **endothelial** growth factor (VEGF) but not basic fibroblast growth factor (bFGF). Most important, the addition of neutralizing VEGF antibodies completely inhibited the ability of NB4 CM to stimulate **endothelial cell** migration, suggesting that APL angiogenesis is mediated by VEGF. The effect of all-trans **retinoic** acid (ATRA) on APL angiogenesis was then studied. ATRA **therapy** resulted in a decrease in bone marrow microvessel density and hot spot density. CM from ATRA-treated APL **cells** did not stimulate **endothelial cell** migration. Finally, quantitative assays showed that ATRA treatment resulted in the abrogation of VEGF production by the NB4 **cells**. These results show that there is increased angiogenesis and VEGF production in APL and that ATRA **therapy** inhibits VEGF production and suppresses angiogenesis. The addition of specific antiangiogenic agents to differentiation **therapy** or chemotherapy should be explored. (Blood. 2001;97:3919-3924)

5/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11189164 21212046 PMID: 11312106
Endogenous angiogenesis inhibitors and their **therapeutic** implications.
Cao Y
Laboratory of Angiogenesis Research, Microbiology and Tumor Biology Center, Karolinska Institute, S-171 77, Stockholm, Sweden. yihai.cao@mtc.ki.se
international journal of biochemistry & cell biology (England) Apr **2001**, 33 (4) p357-69, ISSN 1357-2725 Journal Code: 9508482
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A number of endogenous inhibitors targeting the tumor vasculature have recently been identified using in vitro and in vivo antiangiogenesis **models** . While many of these angiogenesis inhibitors display a broad spectrum of biological actions on several systems in the body, several inhibitors including angiostatin, endostatin, and serpin antithrombin seem to act specifically on the proliferating **endothelial cell** compartment of the newly formed blood vessels. The discovery of these specific **endothelial** inhibitors not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological angiogenesis, but may also provide an important **therapeutic** strategy for the treatment of cancer and other angiogenesis dependent diseases, including diabetic **retinopathy** and chronic inflammations. Systemic administration of these angiogenesis inhibitors in animals significantly suppresses the growth of a variety of tumors and their metastases. However, their production as functional recombinant proteins has been proven to be difficult. In addition, high dosages of these inhibitors are required to suppress tumor growth in animal studies. Other disadvantages of the antiangiogenic protein **therapy** include repeated injections, prolonged treatment, transmission of toxins and infectious particles, and high cost for manufacturing large amounts of protein molecules. Thus, alternative strategies need to be developed in order to improve the clinical settings of antiangiogenic **therapy**.

loss.

5/3,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11350170 21417791 PMID: 11526242
An anti-angiogenic state in mice and humans with **retinal** photoreceptor **cell** degeneration.
Lahdenranta J; Pasqualini R; Schlingemann R O; Hagedorn M; Stallcup W B; Bucana C D; Sidman R L; Arap W
University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Aug 28 **2001**, 98 (18) p10368-73, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Abnormal angiogenesis accompanies many pathological conditions including cancer, inflammation, and eye diseases. Proliferative **retinopathy** because of **retinal** neovascularization is a leading cause of blindness in developed countries. Another major cause of irreversible vision loss is **retinitis** pigmentosa, a group of diseases characterized by progressive photoreceptor **cell** degeneration. Interestingly, anecdotal evidence has long suggested that proliferative diabetic **retinopathy** is rarely associated clinically with **retinitis** pigmentosa. Here we show that neonatal mice with classic inherited **retinal** degeneration (Pdeb(rd1)/Pdeb(rd1)) fail to mount reactive **retinal** neovascularization in a mouse **model** of oxygen-induced proliferative **retinopathy** . We also present a comparable human paradigm: spontaneous regression of **retinal** neovascularization associated with long-standing diabetes mellitus occurs when **retinitis** pigmentosa becomes clinically evident. Both mouse and human data indicate that reactive **retinal** neovascularization either fails to develop or regresses when the number of photoreceptor **cells** is markedly reduced. Our findings support the hypothesis that a functional mechanism underlying this anti-angiogenic state is failure of the predicted up-regulation of vascular **endothelial** growth factor, although other growth factors may also be involved. Preventive and **therapeutic** strategies against both proliferative and degenerative **retinopathies** may emerge from this work.

5/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11296934 21335947 PMID: 11442494
Intercellular adhesion molecule-1 in extravasation of normal mononuclear and leukaemia **cells**.
Mustjoki S; Alitalo R; Elonen E; Carpen O; Gahmberg C G; Vaheri A
Departments of Virology, University of Helsinki, Finland. Satu.Mustjoki@helsinki.fi
British journal of haematology (England) Jun **2001**, 113 (4) p989-1000, ISSN 0007-1048 Journal Code: 0372544
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Interaction of intercellular adhesion molecules (ICAMs) with their receptors has a key role in normal leucocyte adhesion and migration, whereas in leukaemia this has not been well established. In this study, we have evaluated the roles of different adhesion molecules in normal and

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*File 155: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.
File 5:Biosis Previews(R) 1969-2002/Jul W3
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*File 5: Alert feature enhanced for multiple files, duplicates removal, customized scheduling. See HELP ALERT.

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5/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13381010 22080186 PMID: 12072560
Adeno-associated virus type-2 expression of pigmented epithelium-derived factor or Kringles 1-3 of angiostatin reduce **retinal** neovascularization.
Raisler Brian J; Berns Kenneth I; Grant Maria B; Beliaev Denis; Hauswirth William W
Department of Ophthalmology, Box 100284, University of Florida, Gainesville, FL 32610-0284, USA.
Proceedings of the National Academy of Sciences of the United States of America (United States) Jun 25 **2002**, 99 (13) p8909-14, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: EY11123; EY; NEI; EY13729; EY; NEI; NS36302; NS; NINDS; T32EY07043; EY; NEI
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Neovascular diseases of the **retina** include age-related macular degeneration and diabetic **retinopathy**, and together they comprise the leading causes of adult-onset blindness in developed countries. Current surgical, pharmaceutical, and laser **therapies** for age-related macular degeneration (AMD) rarely result in improved vision, do not significantly prevent neovascularization (NV), and often result in at least some vision loss. To address this **therapeutic** gap, we determined the efficacy of recombinant adeno-associated viral (rAAV) serotype-2-mediated expression of pigment epithelium-derived factor (PEDF) or Kringle domains 1-3 of angiostatin (K1K3) in reducing aberrant vessel formation in a mouse **model** of ischemia-induced **retinal** NV. Both PEDF and K1K3 are potent inhibitors of NV when injected directly, hence expression of these **therapeutic** factors from rAAV may provide long-term protection from neovascular eye disease. rAAV vectors expressing the **therapeutic** gene were injected into one eye of postnatal day 0 (P0) newborn mouse pups. **Retinal** NV was induced in P7 mice by exposure to elevated oxygen for 5 days followed by room air for another five days. **Retinal** NV was quantified by the number of vascular-**endothelial**-**cell** nuclei above the inner-limiting membrane in P17 eyes. The number of such vascular **endothelial cell** nuclei in eyes treated with rAAV-PEDF or rAAV-K1K3 was significantly reduced (both $P < 0.0000002$) compared with control eyes. Ocular protein levels detected by ELISA correlate well with the reduction in NV and confirm that expression of antineovascular agents from rAAV vectors may be a **therapeutically** useful treatment of **retinal** or choroidal neovascular disease.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13370214 22061819 PMID: 12067070
Angiostatic proteins and peptides.
Bouma-ter Steege J C; Mayo K H; Griffioen A W
Department of Internal Medicine, University Hospital Maastricht, The Netherlands.
Critical reviews in eukaryotic gene expression (United States) **2001**, 11 (4) p319-34, ISSN 1045-4403 Journal Code: 9007261
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Angiogenesis, or the formation of new vasculature out of preexisting capillaries, is a sequence of events that is essential in the normal physiological processes of tissue growth and in a broad spectrum of pathologies. The diseases in which angiogenesis plays a key role are divided into diseases that are characterized by hypoxia/ ischemia and diseases that are dependent on neovascularization. The formerpathologies may benefit from **therapeutic** angiogenesis stimulation. This review concentrates on the different strategies to inhibit angiogenesis in diseases that are characterized by excessive angiogenesis, for example, cancer, arthritis, diabetic **retinopathy**, and inflammatory diseases. These diseases are dependent on the development of newvasculature, and hence, a large variety of different strategies to inhibit angiogenesis are underwayin laboratories throughout the world. At present, over250 angiogenesis inhibitors are described, and approximately half of them display activity in in vivo **models**. A large percentage of these molecules are natural, nonnatural, or synthetic so-called small molecules. Others are of protein origin, either endogenous or exogenous by nature. The authors highlight the current knowledge on the development of angiostatic proteins and peptides and their potential in the treatment of disease.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13362136 22086097 PMID: 12091447
Regression of ocular neovascularization in response to increased expression of pigment epithelium-derived factor.
Mori Keisuke; Gehlbach Peter; Ando Akira; McVey Duncan; Wei Lisa; Campochiaro Peter A
Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287-9277, USA.
Investigative ophthalmology & visual science (United States) Jul **2002**, 43 (7) p2428-34, ISSN 0146-0404 Journal Code: 7703701
Contract/Grant No.: EY05951; EY; NEI; EY12609; EY; NEI; K08 EY13420; EY; NEI; P30EY1765; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Several pharmacologic treatments have been shown to reduce ocular neovascularization when administered before the onset of angiogenic stimuli, but none have been shown to cause regression of already established ocular neovascularization. In this study, the authors tested the effect of adenoviral vectored pigment epithelium-derived factor (PEDF) gene transfer on established neovascularization in transgenic mice with expression of vascular **endothelial** growth factor (VEGF) in photoreceptors (rho/VEGF mice) and in a **model** of choroidal neovascularization. METHODS: Two weeks after the onset of VEGF transgene expression in rho/VEGF mice or 2 weeks after laser-induced rupture of Bruch's membrane in wild-type mice, subgroups of mice were killed, and the baseline amount of neovascularization was measured by image analysis. The remainder of the mice received an intravitreous or subretinal injection of adenoviral vector containing a PEDF expression construct (AdPEDF.11) or control vector (AdNull.11). RESULTS: Seven days after injection in rho/VEGF mice or 10 days after injection in the choroidal neovascularization **model** , the amount of neovascularization in AdPEDF.11-injected eyes was significantly less than the baseline level, indicating that regression of neovascularization had occurred. There was TUNEL staining within choroidal neovascular lesions in eyes injected with AdPEDF.11. Eyes given a subretinal injection of AdNull.11 had TUNEL-positive **cells** in the **retina** , but none within areas of choroidal neovascularization. CONCLUSIONS: These data indicate that increased expression of PEDF causes regression of ocular neovascularization by promoting apoptosis of **cells** within neovascular lesions and possibly represents a new treatment paradigm for patients with established ocular neovascularization.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13331023 21645779 PMID: 11786424
Synthetic peptides interacting with the 67-kd laminin receptor can reduce **retinal** ischemia and inhibit hypoxia-induced **retinal** neovascularization.
Gebarowska Dorota; Stitt Alan W; Gardiner Thomas A; Harriott Patrick; Greer Brett; Nelson John
Centre of Ophthalmology and Vision Science and the School of Biology and Biochemistry, The Queen's University of Belfast, Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom.
American journal of pathology (United States) Jan **2002**, 160 (1) p307-13, ISSN 0002-9440 Journal Code: 0370502
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed

The high-affinity 67-kd laminin receptor (67LR) is expressed by proliferating **endothelial cells** during **retinal** neovascularization. The role of 67LR has been further examined experimentally by administration of selective 67LR agonists and antagonists in a murine **model of proliferative retinopathy**. These synthetic 67LR ligands have been previously shown to stimulate or inhibit **endothelial cell** motility in vitro without any direct effect on proliferation. In the present study, a fluorescently labeled 67LR antagonist (EGF(33-42)) was injected intraperitoneally into mice and its distribution in the **retina** was assessed by confocal scanning laser microscopy. Within 2 hours this peptide was localized to the **retinal** vasculature, including preretinal neovascular complexes, and a significant amount had crossed the blood **retinal** barrier. For up to 24 hours postinjection, the peptide was still present in the **retinal** vascular walls and, to a lesser extent, in the neural **retina**. Non-labeled EGF(33-42) significantly inhibited pre-**retinal** neovascularization in comparison to controls treated with phosphate-buffered saline or scrambled peptide ($P < 0.0001$). The agonist peptide (Lam beta 1(925-933)) also significantly inhibited proliferative **retinopathy**; however, it caused a concomitant reduction in **retinal** ischemia in this **model** by promoting significant revascularization of the central **retina** ($P < 0.001$). Thus, 67LR appears to be an important target receptor for the modulation of **retinal** neovascularization. Agonism of this receptor may be valuable in reducing the hypoxia-stimulated release of angiogenic growth factors which drives **retinal** angiogenesis.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13242929 21856941 PMID: 11866542

Advanced glycation end products induce angiogenesis in vivo.

Okamoto Tamami; Tanaka Shinya; Stan Alex C; Koike Takao; Kase Manabu; Makita Zenji; Sawa Hirofumi; Nagashima Kazuo

Laboratory of Molecular & Cellular Pathology, Hokkaido University School of Medicine, N 15, W7, Kita-ku, Sapporo, 060-8638, Japan.

Microvascular research (United States) Mar **2002**, 63 (2) p186-95, ISSN 0026-2862 Journal Code: 0165035

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Advanced glycation end products (AGEs) have been thought to participate in diabetic microangiopathy. However, the effects of AGEs on angiogenesis have so far been mainly examined either in vitro or by using cultured **cells** . In the present study, we have analyzed whether AGEs induce angiogenesis in vivo by using the chorioallantoic membrane (CAM) assay. The CAM assay was carried out in embryonated hen eggs to determine the effects of AGEs. Following generation of AGEs based on bovine serum albumin (BSA), either AGE-BSA or nonglycated BSA was administered to the CAM and their effects on angiogenesis were assessed, together with an inhibitory effect of an anti-AGE antibody against AGE-BSA-induced angiogenesis. The histological features of AGE-induced vascular lumens were examined by immunohistochemical analysis for Factor VIII and smooth muscle alpha-actin. AGE-BSA induced angiogenesis in CAM in a dose- and time-dependent manner. AGE-induced angiogenesis on CAM was neutralized by the anti-AGE antibody. Immunohistochemical analysis demonstrated that AGE-induced vascular lumens were devoid of pericytes. Our data demonstrated that AGEs are an angiogenetic factor and that our system of AGE-induced abnormal vessels in CAMs is useful in further investigations of the mechanism of diabetic **retinal** angiogenesis and can also be used to provide a **therapeutic model** for diabetic angiopathy.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13232862 21571851 PMID: 11714448
A potential use of a synthetic **retinoid** TAC-101 as an orally active agent that blocks angiogenesis in liver metastases of human stomach cancer **cells**.
Oikawa T; Murakami K; Sano M; Shibata J; Wierzba K; Yamada Y
Pharmaceutical Research and Development Center, The Tokyo Metropolitan Institute of Medical Science (Rinshoken), Tokyo Metropolitan Organization for Medical Research, Bunkyo-ku, Tokyo 113-8613. oikawa@rinshoken.or.jp
Japanese journal of cancer research : Gann (Japan) Nov **2001**, 92 (11) p1225-34, ISSN 0910-5050 Journal Code: 8509412
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
TAC-101 (4-[3,5-bis(trimethylsilyl)benzamido]benzoic acid) is a novel, synthetic **retinoid** that is effective against liver metastases of human gastrointestinal cancer **cells** such as the human stomach carcinoma line AZ-521 in animal **models**, and is currently in use in phase I cancer trials. However, the mechanism of its antimetastatic action is still poorly understood. Tumor metastasis depends on angiogenesis, and various **retinoids** have been found to exhibit antiangiogenic activity. Based on these findings we here examined the antiangiogenic effects of TAC-101. Oral administration of TAC-101 (2-8 mg/kg/day) resulted in a drastic suppression of the AZ-521 **cell**-induced angiogenesis in a mouse dorsal air sac assay system, compared to the vehicle alone. Immunohistochemical analysis with antibody against the **endothelial** marker CD31 revealed a significant reduction in microvessel density in liver metastases from animals treated with TAC-101 (8 mg/kg p.o.), compared to liver metastases from the untreated control animals. The ability of TAC-101 (8 mg/kg p.o.) to prevent experimental liver metastasis of AZ-521 **cells** in athymic nude mice was comparable with that of the known angiogenesis inhibitor TNP-470 (30 mg/kg s.c.). TAC-101 also affected angiogenesis in chorioallantoic membranes and some functions of **endothelial cells** associated with angiogenesis, whereas the **retinoid** failed to suppress AZ-521 **cell** proliferation directly. These data suggest that the TAC-101 is an orally active antiangiogenic agent and that this antiangiogenic property may contribute to its efficacy against liver metastasis of human stomach cancer **cells**.

5/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13146523 21935220 PMID: 11938451
Inhibition of **retinal** neovascularisation by gene transfer of soluble VEGF receptor sFlt-1.
Bainbridge J W B; Mistry A; De Alwis M; Paleolog E; Baker A; Thrasher A J ; Ali R R
Department of Molecular Genetics, Institute of Ophthalmology, University College London, London, UK.
Gene therapy (England) Mar **2002**, 9 (5) p320-6, ISSN 0969-7128 Journal Code: 9421525
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Retinal angiogenesis is a central feature of the leading causes of blindness. Current treatments for these conditions are of limited efficacy and cause significant adverse effects. In this study, we evaluated the angiostatic effect of gene transfer of the soluble VEGF receptor sFlt-1 in

a mouse **model** of ischaemia-induced **retinal** neovascularisation using adenovirus and adeno-associated virus (AAV) vectors. We induced proliferative **retinopathy** in mice by exposure to 75% oxygen from postnatal day 7 (p7) to p12 and injected intravitreally recombinant viral vectors expressing the reporter green fluorescent protein (GFP) or vectors expressing the VEGF inhibitor sFlt-1. Efficient adenovirus-mediated GFP expression was evident in **cells** of the corneal endothelium and iris pigment epithelium. AAV-mediated GFP expression was evident in ganglion **cells** and **cells** of the inner nuclear layer of the **retina**. Vector-mediated sFlt-1 expression was confirmed by ELISA of pooled homogenised whole eyes. Injection of either vector expressing sFlt-1 resulted in a reduction in the number of neovascular **endothelial** **cells** by 56% and 52% for adenovirus and AAV vectors, respectively (P < 0.05). Local gene transfer of sFlt-1 consistently inhibits experimental **retinal** neovascularisation by approximately 50% and offers a powerful novel approach to the clinical management of **retinal** neovascular disorders.

5/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13054844 21898400 PMID: 11901189
Acute intensive insulin **therapy** exacerbates diabetic blood-**retinal** barrier breakdown via hypoxia-inducible factor-1alpha and VEGF.

Poulaki Vassiliki; Qin Wenying; Joussen Antonia M; Hurlbut Peter; Wiegand Stanley J; Rudge John; Yancopoulos George D; Adamis Anthony P
Laboratory of Surgical Research, Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Journal of clinical investigation (United States) Mar **2002**, 109 (6) p805-15, ISSN 0021-9738 Journal Code: 7802877
Contract/Grant No.: EY 11627; EY; NEI; EY 12611; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Acute intensive insulin **therapy** is an independent risk factor for diabetic **retinopathy** . Here we demonstrate that acute intensive insulin **therapy** markedly increases VEGF mRNA and protein levels in the **retinae** of diabetic rats. **Retinal** nuclear extracts from insulin-treated rats contain higher hypoxia-inducible factor-1alpha (HIF-1alpha) levels and demonstrate increased HIF-1alpha-dependent binding to hypoxia-responsive elements in the VEGF promoter. Blood-**retinal** barrier breakdown is markedly increased with acute intensive insulin **therapy** but can be reversed by treating animals with a fusion protein containing a soluble form of the VEGF receptor Flt; a control fusion protein has no such protective effect. The insulin-induced **retinal** HIF-1alpha and VEGF increases and the related blood-**retinal** barrier breakdown are suppressed by inhibitors of p38 mitogen-activated protein kinase (MAPK) and phosphatidylinositol (PI) 3-kinase, but not inhibitors of p42/p44 MAPK or protein kinase C. Taken together, these findings indicate that acute intensive insulin **therapy** produces a transient worsening of diabetic blood-**retinal** barrier breakdown via an HIF-1alpha-mediated increase in **retinal** VEGF expression. Insulin-induced VEGF expression requires p38 MAPK and PI 3-kinase, whereas hyperglycemia-induced VEGF expression is HIF-1alpha-independent and requires PKC and p42/p44 MAPK. To our knowledge, these data are the first to identify a specific mechanism for the transient worsening of diabetic **retinopathy**, specifically blood-**retinal** barrier breakdown, that follows the institution of intensive insulin **therapy**.

5/3,AB/9 (Item 9 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13010801 21856773 PMID: 11866530
Solution structure of a phage-derived peptide antagonist in complex with vascular **endothelial** growth factor.
Pan Borlan; Li Bing; Russell Stephen J; Tom Jeffrey Y K; Cochran Andrea G ; Fairbrother Wayne J
Department of Protein Engineering, Genentech Inc., South San Francisco, CA 94080, USA.
Journal of molecular biology (England) Feb 22 **2002**, 316 (3) p769-87, ISSN 0022-2836 Journal Code: 2985088R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Vascular **endothelial** growth factor (VEGF) is a potent **endothelial cell** -specific mediator of angiogenesis and vasculogenesis. VEGF is involved pathologically in cancer, proliferative **retinopathy** and rheumatoid arthritis, and as such represents an important **therapeutic** target. Three classes of disulfide-constrained peptides that antagonize binding of the VEGF dimer to its receptors, KDR and Flt-1, were identified previously using phage display methods. NMR studies of a representative peptide from the most potent class of these peptide antagonists, v107 (GGNECDAIRMWEWECFERL), were undertaken to characterize its interactions with VEGF. v107 has no defined structure free in solution, but binding to VEGF induces folding of the peptide. The solution structure of the VEGF receptor-binding domain-v107 complex was determined using 3940 (1970 per VEGF monomer) internuclear distance and 476 (238 per VEGF monomer) dihedral angle restraints derived from NMR data obtained using samples containing either (13)C/(15)N-labeled protein plus excess unlabeled peptide or (13)C/(15)N-labeled peptide plus excess unlabeled protein. Residual dipolar coupling restraints supplemented the structure determination of the complex and were found to increase significantly both the global precision of VEGF in the complex and the agreement with available crystal structures of VEGF. The calculated ensemble of structures is of high precision and is in excellent agreement with the experimental restraints. v107 has a turn-helix conformation with hydrophobic residues partitioned to one face of the peptide and polar or charged residues at the other face. Contacts between two v107 peptides and the VEGF dimer are mediated by primarily hydrophobic side-chain interactions. The v107-binding site on VEGF overlaps partially with the binding site of KDR and is similar to that for domain 2 of Flt-1. The structure of the VEGF-v107 complex provides new insight into how binding to VEGF can be achieved that may be useful for the design of small molecule antagonists. Copyright 2002 Elsevier Science Ltd.

5/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12983694 21856622 PMID: 11867604
Pigment epithelium-derived factor suppresses ischemia-induced **retinal** neovascularization and VEGF-induced migration and growth.
Duh Elia J; Yang Hoseong S; Suzuma Izumi; Miyagi Masaru; Youngman Elaine; Mori Keisuke; Katai Miyuki; Yan Lin; Suzuma Kiyoshi; West Karen; Davarya Shekar; Tong Patrick; Gehlbach Peter; Pearlman Joel; Crabb John W; Aiello Lloyd P; Campochiaro Peter A; Zack Donald J
Department of Ophthalmology, Johns Hopkins University School of Medicine, Maumenee 809, 600 N. Wolfe Street, Baltimore, MD 21287, USA.
Investigative ophthalmology & visual science (United States) Mar **2002**, 43 (3) p821-9, ISSN 0146-0404 Journal Code: 7703701
Contract/Grant No.: EY 00398; EY; NEI; EY 01765; EY; NEI; EY 06603; EY; NEI
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To determine the effect of pigment epithelium-derived factor (PEDF) in a mouse **model** of ischemia-induced **retinal** neovascularization and on vascular **endothelial** growth factor (VEGF)--induced migration and growth of cultured microvascular **endothelial cells** . METHODS: Human recombinant PEDF was expressed in the human embryonic kidney 293 **cell** line and purified by ammonium sulfate precipitation and cation exchange chromatography. C57BL/6 mice were exposed to 75% oxygen from postnatal day (P)7 to P12 and then returned to room air. Mice received intravitreal injections of 2 microg PEDF in one eye and vehicle in the contralateral eye on P12 and P14. At P17, mice were killed and eyes enucleated for quantitation of **retinal** neovascularization. The mitogenic and motogeneic effects of VEGF on cultured bovine **retinal** and adrenal capillary **endothelial cells** were examined in the presence or absence of PEDF, using **cell** counts and migration assays. RESULTS: Two species of human recombinant PEDF, denoted A and B, were purified to apparent homogeneity. PEDF B appeared to comigrate on SDS-PAGE with PEDF from human vitreous samples. Changes in electrophoretic mobility after peptide-N-glycosidase F (PNGase F) digestion suggest that both PEDF forms contain N-linked carbohydrate. Analyses of the intact proteins by liquid chromatography-electrospray mass spectrometry (LC-ESMS) revealed the major molecular weight species for PEDF A (47,705 +/- 4) and B (46,757 +/- 5). LC-ESMS analysis of tryptic peptides indicated that PEDF A and B exhibit differences in glycopeptides containing N-acetylneuraminic acid (NeuAc) and N-acetylhexosamine (HexNAc). Intravitreal administration of either species of PEDF significantly inhibited **retinal** neovascularization (83% for PEDF A and 55% for PEDF B; P = 0.024 and 0.0026, respectively). PEDF A and B (20 nM) suppressed VEGF-induced **retinal** microvascular **endothelial cell** proliferation by 48.8% and 41.4%, respectively, after 5 days (P < 0.001) and VEGF-induced migration by 86.5% +/- 16.7% and 78.1% +/- 22.3%, respectively, after 4 hours (P = 0.004 and P = 0.008, respectively). CONCLUSIONS: These data indicate that elevated concentrations of PEDF inhibit VEGF-induced **retinal endothelial cell** growth and migration and **retinal** neovascularization. These findings suggest that localized administration of PEDF may be an effective approach for the treatment of ischemia-induced **retinal** neovascular disorders.

5/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12972220 21574758 PMID: 11718257
Magnetic resonance imaging of ethyl-nitrosourea-induced rat gliomas: a **model** for experimental **therapeutics** of low-grade gliomas.
Kish P E; Blaivas M; Strawderman M; Muraszko K M; Ross D A; Ross B D; McMahon G
Department of Neurosurgery, University of Michigan Medical School, Ann Arbor 48109-0338, USA. pkish@umich.edu
Journal of neuro-oncology (Netherlands) Jul **2001**, 53 (3) p243-57, ISSN 0167-594X Journal Code: 8309335
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human low-grade gliomas represent a population of brain tumors that remain a **therapeutic** challenge. Preclinical evaluation of agents, to test their preventive or **therapeutic** efficacy in these tumors, requires the use of animal **models**. Spontaneous gliomas develop in **models** of chemically induced carcinogenesis, such as in the transplacental N-ethyl-N-nitrosourea (ENU) rat **model** . However,

without the ability to detect initial tumor formation, multiplicity or to measure growth rates, it is difficult to test compounds for their interventional or preventional capabilities. In this study Fisher-334 rats, treated transplacentally with ENU, underwent magnetic resonance imaging (MRI) examination in order to evaluate this approach for detection of tumor formation and growth. ENU-induced intracranial cerebral tumors were first observable in T2-weighted images beginning at 4 months of age and grew with a mean doubling time of 0.487 +/- 0.112 months. These tumors were found histologically to be predominately mixed gliomas. Two **therapeutic** interventions were evaluated using MRI, vitamin A (all-trans **retinol** palmitate, RP), as a chemopreventative agent and the anti-angiogenic drug SU-5416. RP was found to significantly delay the time to first tumor observation by one month (P = 0.05). No differences in rates of tumor formation or growth rates were observed between control and RP-treated groups. MRI studies of rats treated with SU-5416 resulted in reduction in tumor growth rates compared to matched controls. These results show that MRI can be used to provide novel information relating to the **therapeutic** efficacy of agents against the ENU-induced tumor **model**.

5/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12959224 21520400 PMID: 11642726

Vascular **endothelial** growth factor (VEGF), transforming growth factor-beta (TGFbeta), and interleukin-6 (IL-6) in experimental herpesvirus **retinopathy**: association with inflammation and viral infection.

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Histology and histopathology (Spain) Oct **2001**, 16 (4) p1061-71
, ISSN 0213-3911 Journal Code: 8609357

Contract/Grant No.: EY 05475; EY; NEI; EY 05951; EY; NEI; EY 10017; EY; NEI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Experimental herpesvirus **retinopathy** presents a unique **model** of a transient inflammatory response in the virus-injected eye and subsequent acute **retinal** necrosis and chronic inflammation in the contralateral eye. For 6 days after infection, VEGF, TGFbeta1, and TGFbeta2 were associated only with inflammatory **cells** in the injected eye. By 6 days (after viral antigens were no longer detected), VEGF and TGFbeta2 were upregulated in **retinas** of injected eyes until 8-10 days. In contralateral eyes, VEGF was first demonstrated in the **retina** at 6-7 days (prior to the appearance of viral antigens) and TGFbeta2 at 7-8 days. Staining for these factors was also evident around areas of necrosis. The VEGF receptor, flt-1, was associated with ganglion **cells** and the inner nuclear layer of normal and experimental mice and it was also demonstrated around areas of necrosis. Another VEGF receptor, flk-1, was localized to Muller **cell** processes and the outer plexiform layer in normal and experimental mice. Coincident with VEGF upregulation in the **retinas** of herpesvirus-1 injected mice, there was increased flk-1 in ganglion **cells** and the inner and outer nuclear layers. IL-6 was associated with Muller **cell** endfeet in normal mice. Following unilateral intraocular inoculation, IL-6 spread along the MUller **cell** processes and some astrocytes demonstrated IL-6 in both eyes at 6-8 days. The present study demonstrates that intraocular inoculation of herpesvirus is sufficient to induce VEGF, flk-1, TGFbeta2, and IL-6 in the **retinas** of injected and contralateral eyes. Further investigation of common signaling pathways for these factors during responses to viral

infection and the development of acute **retinal** necrosis could provide information useful for **therapeutic** intervention in human herpesvirus **retinopathy**.

5/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12948866 21575987 PMID: 11719828
Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy.
Cameron N E; Eaton S E; Cotter M A; Tesfaye S
Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen, Scotland, United Kingdom.
Diabetologia (Germany) Nov **2001**, 44 (11) p1973-88, ISSN 0012-186X Journal Code: 0006777
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Diabetes mellitus is a major cause of peripheral neuropathy, commonly manifested as distal symmetrical polyneuropathy. This review examines evidence for the importance of vascular factors and their metabolic substrate from human and animal studies. Diabetic neuropathy is associated with risk factors for macrovascular disease and with other microvascular complications such as poor metabolic control, dyslipidaemia, body mass index, smoking, microalbuminuria and **retinopathy**. Studies in human and animal **models** have shown reduced nerve perfusion and endoneurial hypoxia. Investigations on biopsy material from patients with mild to severe neuropathy show graded structural changes in nerve microvasculature including basement membrane thickening, pericyte degeneration and **endothelial cell** hyperplasia. Arterio-venous shunting also contributes to reduced endoneurial perfusion. These vascular changes strongly correlate with clinical defects and nerve pathology. Vasodilator treatment in patients and animals improves nerve function. Early vasa nervorum functional changes are caused by the metabolic insults of diabetes, the balance between vasodilation and vasoconstriction is altered. Vascular endothelium is particularly vulnerable, with deficits in the major **endothelial** vasodilators, nitric oxide, endothelium-derived hyperpolarising factor and prostacyclin. Hyperglycaemia and dyslipidaemia driven oxidative stress is a major contributor, enhanced by advanced glycation end product formation and polyol pathway activation. These are coupled to protein kinase C activation and omega-6 essential fatty acid dysmetabolism. Together, this complex of interacting metabolic factors accounts for **endothelial** dysfunction, reduced nerve perfusion and function. Thus, the evidence emphasises the importance of vascular dysfunction, driven by metabolic change, as a cause of diabetic neuropathy, and highlights potential **therapeutic** approaches.

5/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12915372 21839490 PMID: 11850530
Preclinical evaluation of a phosphorothioate oligonucleotide in the **retina** of rhesus monkey.
Shen Wei-Yong; Garrett Kerryn L; Wang Chang-Guan; Zhang Kun; Ma Zhi-Zhong ; Constable Ian J; Rakoczy P Elizabeth
Centre for Ophthalmology and Visual Sciences, University of Western Australia.
Laboratory investigation; a journal of technical methods and pathology (United States) Feb **2002**, 82 (2) p167-82, ISSN 0023-6837 Journal Code: 0376617
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Overexpression of vascular **endothelial** growth factor (VEGF) has been strongly implicated in the development of choroidal neovascularization (CNV) in patients with age-related macular degeneration. In this study, a phosphorothioate oligonucleotide (PS-oligo) targeting both human and rat VEGF(165) genes upstream of the translation initiation code, named DS135 in this study, was evaluated for its uptake dynamics and **retinal** tolerance after intravitreal (IV) and subretinal (SR) injections in the rhesus monkey. Intravitreal and SR injections of a fluorescent-labeled DS135 (FL-DS135) resulted in both dose- and time-dependent uptake and persistence, and FL-DS135 remained detectable in the **retina** for at least 3 weeks after injection. Ophthalmic examination showed transient vitreous haze after IV delivery of a high dose but not with a low dose of FL-DS135. Histologic examination showed no evidence of **retinal** degeneration with respect to IV delivery. After SR delivery, however, dose-related **cellular** infiltration, transient residual fluid, and slight distortion of the neuroretina were observed. The biologic efficacy of DS135 was further assessed in a laser-induced CNV **model**, and development of CNV was determined by fluorescein angiography and histologic examination. Incomplete inhibition of CNV formation was observed after IV and SR injection of DS135, but no statistically significant difference was achieved when compared with dose-matched control of PS-oligo. Analysis of fluorescein angiogram and histologic examination showed less than 30% incidence of CNV development in this monkey **model** . Our study demonstrated that PS-oligos can be successfully introduced into the **retina** , although with potential limitations, after SR delivery. DS135, a PS-oligo targeting the VEGF gene upstream of the translation initiation code, partially inhibited CNV formation. An improved CNV **model** is necessary for further confirmation of the full **therapeutic** potency of DS135 before clinical application.

5/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12873771 21520052 PMID: 11642380

Photodynamic **therapy** of experimental choroidal neovascularization with a hydrophilic photosensitizer: mono-L-aspartyl chlorin e6.

Mori K; Yoneya S; Anzail K; Kabasawa S; Sodeyama T; Peyman G A; Moshfeghi D M

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Retina (Philadelphia, Pa.) (United States) **2001**, 21 (5) p499-508, ISSN 0275-004X Journal Code: 8309919

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

PURPOSE: To demonstrate the selective localization of the hydrophilic photosensitizer mono-L-aspartyl chlorin e6 (NPe6) in experimental choroidal neovascularization in nonhuman primate eyes. METHODS: Sixty-seven experimental choroidal neovascular lesions (CNV) were created in the fundi of Macaca monkeys using the modified Ryan's **model** and documented by fluorescein and indocyanine green angiography. To determine the biodistribution of NPe6 and the optimal timing of laser irradiation after dye administration, NPe6 angiography and fluorescence microscopy with NPe6 were performed. Photodynamic **therapy** (PDT) was performed at various dye doses (0.5-10.0 mg/kg) and laser fluences (7.5-225.0 J/cm2) on the CNV and on 10 areas of normal **retina** and choroid. Treatment outcomes were assessed by fluorescein and indocyanine green angiography and confirmed by light and electron microscopy. RESULTS: NPe6 fluorescence microscopy demonstrated intense fluorescence of CNV and **retinal** pigment

epithelial **cells**. Choroidal vessel walls and outer **retina** adjacent to CNV fluoresced moderately; **retinal** vessel walls and microcapillaries had trace fluorescence. The fluorescence of CNV lesions on fluorescein angiography became stronger than that of **retinal** vessels 20-60 minutes after dye injection. Choroidal neovascular lesion closure was achieved with NPe6 PDT without significant damage to the sensory **retina**. Histology demonstrated necrosis of CNV **endothelial cells** with minimal damage to surrounding tissues. CONCLUSIONS: NPe6 PDT selectively localizes to experimental CNV in nonhuman primates, resulting in occlusion of CNV with sparing of the neurosensory **retina** .

5/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12841396 21676539 PMID: 11818397
Differential effects of bactericidal/permeability-increasing protein (BPI) analogues on **retinal** neovascularization and **retinal** pericyte growth.
Rauniyar Ravi K; Suzuma Kiyoshi; King Adam L; Aiello Lloyd Paul; King George L
Research Division, Joslin Diabetes Center, Boston, Massachusetts 02215, USA.
Investigative ophthalmology & visual science (United States) Feb **2002**, 43 (2) p503-9, ISSN 0146-0404 Journal Code: 7703701
Contract/Grant No.: EY5110; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Bactericidal/permeability-increasing protein (BPI), an antibacterial and lipopolysaccharide-neutralizing protein, also has an antiangiogenic effect. To evaluate the **therapeutic** role of BPI in ischemic **retinopathies** , the antiangiogenic activity of a human recombinant 21-kDa modified N-terminal fragment of BPI (rBPI(21)), which has the biological properties of the holoprotein, and a peptidomimetic (XMP.Z) derived from BPI were examined. METHODS: The effects of rBPI(21) and XMP.Z on VEGF-induced growth of bovine **retinal** microvascular **endothelial cells** (BRECs) and on serum-induced growth of bovine **retinal** pericytes (BRPs) and **retinal** pigment epithelial **cells** (BRPECs) were evaluated by determining total DNA content. The neonatal mouse **model** of **retinopathy** of prematurity (ROP) was used to study the effect of XMP.Z in vivo. Intraperitoneal injections of the peptidomimetic (10 mg/kg) were administered every 24 hours for 5 days (postnatal [P]12-P17) during induction of neovascularization. **Retinal** neovascularization was evaluated using flatmounts of fluorescein-dextran-perfused **retinas** and quantitated by counting **retinal cell** nuclei anterior to the internal limiting membrane. RESULTS. VEGF (25 ng/mL) increased the total DNA per well of BRECs by 120% +/- 50% ($P < 0.001$), which was inhibited by addition of rBPI(21) or XMP.Z, with decreases of 77% +/- 15% ($P < 0.05$) and 107% +/- 19% ($P < 0.01$) at maximum effective doses of 75 and 15 microg/mL rBPI(21) and XMP.Z, respectively. In contrast, rBPI(21) at 75 microg/mL enhanced the total DNA per well of BRP 53% +/- 14% ($P < 0.001$) in the presence of 5% fetal bovine serum (FBS), whereas XMP.Z enhanced BRP growth by 27% +/- 7% ($P < 0.001$) at 5 microg/mL. In the presence of 10% FBS, rBPI(21) and XMP.Z increased BRP growth by 91% +/- 35% ($P < 0.001$) and 43% +/- 18% ($P < 0.01$), respectively. In the oxygen-induced ROP neonatal mouse **model**, **retinal** neovascularization was decreased by 40% +/- 16% ($n = 5$, $P < 0.01$) when animals were treated with XMP.Z. CONCLUSIONS: Two BPI-derived compounds, rBPI(21) and XMP.Z, significantly suppressed VEGF-induced BREC growth in vitro, while conversely enhancing the growth of BRPs, even above that induced by 20% FBS. When tested in animals, XMP.Z also suppressed

ischemia-induced **retinal** neovascularization in mice. These data suggest that BPI-derived compounds may have unique **therapeutic** potential for proliferative **retinal** diseases such as diabetic **retinopathy** , if physiological levels can be achieved in clinical settings.

5/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12798266 21420348 PMID: 11529667
In vivo use of oligonucleotides to inhibit choroidal neovascularisation in the eye.
Garrett K L; Shen W Y; Rakoczy P E
Department of Molecular Ophthalmology, Lions Eye Institute, Nedlands, Western Australia, Australia.
journal of gene medicine (England) Jul-Aug **2001**, 3 (4) p373-83 , ISSN 1099-498X Journal Code: 9815764
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: We have previously demonstrated the in vivo uptake of oligonucleotides in the rat eye and have continued with experiments to look at the effectiveness of targeted oligonucleotide sequences. Vascular **endothelial** growth factor (VEGF) is correlated with new blood vessel formation and has been implicated in numerous eye diseases characterised by abnormal blood vessel proliferation. An oligonucleotide targeted to the VEGF sequence was examined for its effect on VEGF production in vitro and the development of choroidal neovascularisation in vivo in the eye. METHODS: A series of sequences were assessed in an in vitro screening system using **retinal** pigment epithelial (RPE) **cells** to demonstrate a reduction in VEGF. A targeted sequence was further investigated using an animal **model** of choroidal neovascularisation where a krypton laser was used to produce a wound healing response in the choroid and **retina** . The oligonucleotide was injected into the vitreous and the development of choroidal neovascularisation assessed using fluorescein angiography. RESULTS: The targeted sequence was shown in vitro to downregulate the VEGF produced by RPE **cells** grown under hypoxic conditions and when injected into laser treated eyes was shown to be preferentially taken up in the laser lesion. Fluorescein angiography demonstrated that the test oligonucleotide was successful in reducing laser-mediated choroidal neovascularisation. CONCLUSIONS: A sequence corresponding to the 5'UTR of the VEGF gene has provided encouraging results for the treatment of neovascularisation.

5/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12795273 21634508 PMID: 11772931
Angioprevention': angiogenesis is a common and key target for cancer chemopreventive agents.
Tosetti Francesca; Ferrari Nicolette; De Flora Silvio; Albini Adriana
Molecular Biology Laboratory, National Cancer Research Institute (IST), Genova, Italy.
FASEB journal : official publication of the Federation of American Societies for Experimental Biology (United States) Jan **2002**, 16 (1) p2-14, ISSN 1530-6860 Journal Code: 8804484
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The potential to block tumor growth by inhibition of the neoangiogenic

process represents an intriguing approach to the treatment of solid tumors. The high proliferation rate in the tumor deprived of proper vascularization would be balanced by **cell** death due to lack of diffusion of nutrients and oxygen. Matrix metalloproteinases (MMPs), angiogenic growth factors, and their receptors are the main targets of an increasing number of clinical trials approved to test the tolerance and **therapeutic** efficacy of antiangiogenic agents. We observed that a series of substances proposed as possible cancer chemopreventive agents show antiangiogenic properties when tested in in vitro and in vivo angiogenesis **models**. We demonstrated that N-acetyl-l-cysteine is able to reduce the invasive and metastatic potential of melanoma **cells**, and to inhibit **endothelial cell** invasion by direct inhibition of MMP activity. We also showed that epigallocatechin gallate (EGCG), a flavonoid from green tea that possesses chemopreventive activity in experimental and epidemiological studies, is a potent inhibitor of MMP-2 and MMP-9. Angiogenesis has also been demonstrated to be a target for nonsteroidal anti-inflammatory drug chemopreventive activity. Based on these data, we hypothesize that other chemopreventive agents, including natural or synthetic **retinoids** , steroid hormone antagonists, peroxisome proliferator-activated receptor gamma ligands, vitamin D, and protease inhibitors, might have antiangiogenesis as an important mechanism of action, a novel concept we will term 'angioprevention'. We analyze the mechanisms on how and why chemopreventive agents could exert antiangiogenic effects aimed at controlling tumor growth, and their potential use in the clinic.

5/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12793593 21610487 PMID: 11747139
The role of taurine in diabetes and the development of diabetic complications.
Hansen S H
Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Denmark. shhansen@rh.dk
Diabetes/metabolism research and reviews (England) Sep-Oct **2001**, 17 (5) p330-46, ISSN 1520-7552 Journal Code: 100883450
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The ubiquitously found beta-amino acid taurine has several physiological functions, e.g. in bile acid formation, as an osmolyte by **cell** volume regulation, in the heart, in the **retina** , in the formation of N-chlorotaurine by reaction with hypochlorous acid in leucocytes, and possibly for intracellular scavenging of carbonyl groups. Some animals, such as the cat and the C57BL/6 mouse, have disturbances in taurine homeostasis. The C57BL/6 mouse strain is widely used in diabetic and atherosclerotic animal **models** . In diabetes, the high extracellular levels of glucose disturb the **cellular** osmoregulation and sorbitol is formed intracellularly due to the intracellular polyol pathway, which is suspected to be one of the key processes in the development of diabetic late complications and associated **cellular** dysfunctions. Intracellular accumulation of sorbitol is most likely to cause depletion of other intracellular compounds including osmolytes such as myo-inositol and taurine. When considering the clinical complications in diabetes, several links can be established between altered taurine metabolism and the development of **cellular** dysfunctions in diabetes which cause the clinical complications observed in diabetes, e.g. **retinopathy** , neuropathy, nephropathy, cardiomyopathy, platelet aggregation, **endothelial** dysfunction and atherosclerosis. Possible **therapeutic** perspectives could be a supplementation with taurine and other osmolytes and low-molecular compounds, perhaps in a combinational

therapy with aldose reductase inhibitors. Copyright 2001 John Wiley & Sons, Ltd.

5/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12722540 21583628 PMID: 11726639
Adenosine receptor antagonists and **retinal** neovascularization in vivo.
Mino R P; Spoerri P E; Caballero S; Player D; Belardinelli L; Biaggioni I ; Grant M B
Department of Molecular Biology and Genetics, University of Florida, Gainesville, FL 32610-0267, USA.
Investigative ophthalmology & visual science (United States) Dec **2001**, 42 (13) p3320-4, ISSN 0146-0404 Journal Code: 7703701
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: The role of adenosine receptor (AdoR) antagonists in human **retinal endothelial cell** function in vitro has previously been determined. In this study, efficacy of AdoR antagonist administration in reducing **retinal** neovascularization was examined in a mouse pup **model** of oxygen-induced **retinopathy** . METHODS: A previously described **model** of oxygen-induced **retinal** neovascularization in newborn mouse pups was used to examine the effect of various AdoR antagonists on neovascularization. The nonselective AdoR antagonist xanthine amine congener (XAC), the A(2A)-selective antagonist ZM241385, the A(2B)-selective antagonists 3-N-propylxanthine (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX), and the A(1)-selective antagonist cyclopentyl-1,3-dipropylxanthine (CPX) were used. After the hyperoxia exposure the animals received daily intraperitoneal injections of pharmacologically relevant doses of AdoR antagonists for 5 days. Control animals received vehicle (0.1% dimethyl sulfoxide [DMSO]) alone. The animals were then killed and perfused with fluorescein-dextran. Wholemounts of **retinas** from one eye were prepared and examined, whereas the **retinas** of the contralateral eye were embedded, sectioned, and stained for counting neovascular nuclei extending beyond the internal limiting membrane into the vitreous. RESULTS: Angiography of wholemount **retinas** showed reduction of neovascular tufts in animals treated with selective A(2B) AdoR antagonists. Quantification of the extraretinal neovascular nuclei showed that only animals treated with XAC, enprofylline, or IPDX showed a significant reduction in **retinal** neovascularization. By contrast, neither CPX nor ZM241385 had an effect on neovascularization. CONCLUSIONS: The A(2B)-selective AdoR antagonists inhibited oxygen-induced **retinal** neovascularization in vivo and may provide a basis for developing pharmacologic **therapies** for the treatment of proliferative **retinopathies**.

5/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12695350 21610802 PMID: 11745408
Inhibition of neuroblastoma-induced angiogenesis by fenretinide.
Ribatti D; Alessandri G; Baronio M; Raffaghello L; Cosimo E; Marimpietri D; Montaldo P G; De Falco G; Caruso A; Vacca A; Ponzoni M
Department of Human Anatomy and Histology, University of Bari, Bari, Italy. ribatti@anatomia.uniba.it
International journal of cancer. Journal international du cancer (United States) Nov 1 **2001**, 94 (3) p314-21, ISSN 0020-7136 Journal Code: 0042124
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Retinoids are a class of natural or synthetic compounds that participate in the control of **cell** proliferation, differentiation and fetal development. The synthetic **retinoid** fenretinide (HPR) inhibits carcinogenesis in various animal **models**. **Retinoids** have also been suggested to be effective inhibitors of angiogenesis. The effects of HPR on certain **endothelial cell** functions were investigated in vitro, and its effects on angiogenesis was studied in vivo, by using the chorioallantoic membrane (CAM) assay. HPR inhibited vascular **endothelial** growth factor- (VEGF-) and fibroblast growth factor-2- (FGF-2)-induced **endothelial cell** proliferation without affecting **endothelial** motility; moreover, HPR inhibited growth factor-induced angiogenesis in the CAM assay. Furthermore, a significant antiangiogenic potential of HPR has also been observed in neuroblastoma (NB) biopsy-induced angiogenesis in vivo. We previously demonstrated that supernatants derived from NB **cell** lines stimulated **endothelial cell** proliferation. In the present study, we found that this effect was abolished when NB **cells** were incubated in the presence of HPR. VEGF- and FGF-2-specific ELISA assays, performed on both NB **cells** derived from conditioned medium and **cellular** extracts, indicated no consistent effect of HPR on the level of these angiogenic cytokines. Moreover, RT-PCR analysis of VEGF and FGF-2 gene expression confirmed the above lack of effect. HPR was also able to significantly repress the spontaneous growth of **endothelial cells**, requiring at least 48-72 hr of treatment with HPR, followed by a progressive accumulation of **cells** in G(1) at subsequent time points. Finally, immunohistochemistry experiments performed in the CAM assay demonstrated that **endothelial** staining of both VEGF receptor 2 and FGF-2 receptor-2 was reduced after implantation of HPR-loaded sponges, as compared to control CAMs. These data suggest that HPR exerts its antiangiogenic activity through both a direct effect on **endothelial cell** proliferative activity and an inhibitory effect on the responsivity of the **endothelial cells** to the proliferative stimuli mediated by angiogenic growth factors. Copyright 2001 Wiley-Liss, Inc.

5/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12625496 21568029 PMID: 11711525
Gene **therapy** for cardiovascular disease: a case for cautious optimism.
Khurana R; Martin J F; Zachary I
Center for Cardiovascular Biology and Medicine, Department of Medicine, University College London, London, United Kingdom.
Hypertension (United States) Nov **2001**, 38 (5) p1210-6, ISSN 1524-4563 Journal Code: 7906255
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

There is currently intense interest in the development of gene **therapy** for cardiovascular disease. The stimulation of **therapeutic** angiogenesis for ischemic heart disease has been one of the areas of greatest promise. Encouraging results have been obtained with the angiogenic cytokines vascular **endothelial** growth factor (VEGF) and basic fibroblast growth factor in animal **models**, leading to clinical trials in ischemic heart disease. VEGF also has **therapeutic** potential in a second area of cardiovascular gene **therapy**, the enhancement of arterioprotective **endothelial** functions to prevent postangioplasty restenosis and bypass graft arteriopathy. The

endothelial cell growth and survival functions of VEGF promote **endothelial** regeneration, whereas VEGF-induced **endothelial** production of NO and prostacyclin inhibits vascular smooth muscle **cell** proliferation. Inhibition of neointimal hyperplasia may also be achieved by gene transfer of **endothelial** NO synthase (eNOS), PGI synthase, or **cell** cycle regulators (**retinoblastoma**, cyclin or cyclin-dependent kinase inhibitors, p53, growth arrest homeobox gene, fas ligand) or antisense oligonucleotides to c-myb, c-myc, proliferating **cell** nuclear antigen, and transcription factors such as nuclear factor kappaB and E2F. An improved understanding of etiologically complex pathologies involving the interplay of genes and the environment, such as atherosclerosis and systemic hypertension, has led to the identification of new targets for gene **therapy** , with the potential to alleviate inherited genetic defects such as familial hypercholesterolemia. The use of vasodilator gene overexpression and antisense knockdown of vasoconstrictors to reduce blood pressure in animal **models** of systemic and pulmonary hypertension offers the prospect of gene **therapy** for human hypertensive disease. The renin-angiotensin system has been the target of choice for antihypertensive strategies because of its wide distribution and additional effects on fibrinolytic and oxidative stress pathways. Gene **therapy** in cardiovascular disease has an exciting future but remains at an early stage. Further developments in gene transfer vector technology and the identification of additional target genes will be required before its full **therapeutic** potential can be realized.

5/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12522114 21353965 PMID: 11460014

All-trans **retinoic** acid is partially effective against lipopolysaccharide-induced but not against tissue-factor-induced disseminated intravascular coagulation in rat **models**.

Asakura H; Aoshima K; Ichino T; Suga Y; Saito M; Morishita E; Yamazaki M; Ontachi Y; Mizutani T; Kato M; Miyamoto K I; Nakao S

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Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis (England) Jun **2001**, 12 (4) p301-6,
ISSN 0957-5235 Journal Code: 9102551

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

All-trans **retinoic** acid (ATRA) has been introduced to the management of acute promyelocytic leukemia (APL) as a differentiation treatment. This drug not only causes complete remission, but also improves disseminated intravascular coagulation (DIC) without adding anticoagulants in APL. We have attempted to determine whether ATRA is effective against DIC in rat **models** induced by tissue factor (TF) or lipopolysaccharide (LPS), because the anticoagulant effect of ATRA has been considered to induce thrombomodulin upregulation and TF downregulation on **endothelial cells** as well as on APL **cells**. In male Wistar rats, DIC was induced by a 4-h infusion of thromboplastin (3.75 U/kg) or lipopolysaccharide (30 mg/kg). The rats were given ATRA orally each day at a dose of 100 mg/kg per day for 1 week before the injection of TF or LPS in ATRA treatment groups, or given low molecular weight heparin (LMWH) 10 min before the injection of TF or LPS (200 U/kg, bolus intravenously) in LMWH treatment groups. No significant changes in hemostatic parameters or markers of organ dysfunction were caused by the ATRA administration, while DIC was significantly improved by LMWH in the TF-induced **model**. DIC was significantly improved by both ATRA and LMWH in the LPS-induced **model**. These findings suggested that ATRA was useful for treating DIC only in the LPS-induced **model** , and that drug efficacy should be

carefully assessed because the agents used to induce DIC considerably influenced the outcome.

5/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12515267 21333332 PMID: 11440278
Topical application of integrin antagonists inhibits proliferative **retinopathy**.
Riecke B; Chavakis E; Bretzel R G; Linn T; Preissner K T; Brownlee M; Hammes H P
3rd Medical Department, Justus-Liebig-University Giessen, Germany.
Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme (Germany) May **2001**, 33 (5) p307-11, ISSN 0018-5043 Journal Code: 0177722
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The expression of alphav-integrins is highly selective for angiogenic **endothelial cells** ; ligation inhibition by cyclic RGD peptides prevents pathological neovascularization in tumor or **retinopathy models** to a large extent. We have previously demonstrated that proliferative **retinopathy** in a mouse **model** of **retinopathy** of prematurity (ROP **model**) can be reduced by more than 70%. To minimize systemic side effects and unwanted interference with responsive angiogenesis, we investigated topical application of cyclic RGD-peptides. In preliminary experiments, we could exclude any inhibiting effects of the carrier solution containing EDTA, Na2S, mannitol, hydroxyethyl starch, and benzalconium chloride on the inhibitory effect of cyclic RGD peptides. **Retinal** presence of small molecular-mass integrin antagonists after topical application was confirmed using fluorescein-labeled cyclic RGD peptide. Topical application of the peptide to the eye inhibited proliferative **retinopathy** in a dose-dependent fashion with a maximum of almost 50%. These results suggest that small molecular-mass peptide antagonists of alphav-type integrins are efficient in inhibiting proliferative **retinopathy** by topical application.

5/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12514567 21333423 PMID: 11440369
Intravitreal injection of plasminogen kringle 5, an endogenous angiogenic inhibitor, arrests **retinal** neovascularization in rats.
Zhang D; Kaufman P L; Gao G; Saunders R A; Ma J X
Department of Ophthalmology, Medical University of South Carolina, Charleston 29403, USA.
Diabetologia (Germany) Jun **2001**, 44 (6) p757-65, ISSN 0012-186X Journal Code: 0006777
Contract/Grant No.: EY12231; EY; NEI; EY12600; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
AIMS/HYPOTHESIS: Plasminogen kringle 5 is an endogenous angiogenic inhibitor. The purpose of the present study was to explore the potential application of kringle 5 in the treatment of **retinal** neovascularization. METHODS: Plasminogen kringle 5 was expressed in E. coli and affinity-purified. Its anti-angiogenic activity was determined in cultured primary human capillary **endothelial cells**. **Retinal** neovascularization was induced in newborn rats by exposure to hyperoxia and then normoxia. Kringle 5 was intravitreally injected into the

rat **model**. **Retinal** neovascularization was visualized by fluorescein angiography on flat-mounted **retina** and quantified by counting preretinal vascular **cells**. RESULTS: Plasminogen kringle 5 inhibited primary **endothelial cells** but not **retinal** neuronal **cells**, suggesting **cell** type-specific inhibition. The oxygen-induced **retinopathy** rat **model** showed an over-expression of vascular **endothelial** growth factor, preretinal neovascularization and haemorrhage. Intravitreal injection of kringle 5 before the development of neovascularization resulted in fewer neovascular tufts and pre-**retinal** vascular **cells** than in control rats with PBS injection ($p < 0.01$). Moreover, injection of kringle 5 after the development of neovascularization inhibited the increase in the preretinal vascular **cells** ($p < 0.05$). These results suggest that kringle 5 both prevents the development and arrests the progression of **retinal** neovascularization. The injection of kringle 5 did not result in any detectable inflammatory response in the **retina** or histological toxicity to **retina** neurons and pre-existing vessels. CONCLUSION/INTERPRETATION: These observations suggest that intravitreal delivery of angiogenic inhibitors could have **therapeutic** benefits in neovascular diseases of the **retina**.

5/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11355022 21455426 PMID: 11571574

Hypoxia-inducible transgene expression in differentiated human NT2N neurons--a **cell** culture **model** for gene **therapy** of postischemic neuronal loss.

Cao Y J; Shibata T; Rainov N G

Molecular Neuro-Oncology Laboratory, Department of Neurosurgery, Martin-Luther-University, Halle/S, Germany.

Gene therapy (England) Sep **2001**, 8 (17) p1357-62, ISSN 0969-7128 Journal Code: 9421525

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Expression of anti-apoptotic or neurotrophic transgene proteins in hypoxic neurons may provide a novel **therapeutic** strategy for neuroprotection and alleviation of damage to ischemic brain areas. NT2, a human neoplastic **cell** line which terminally differentiates into postmitotic neurons (NT2N) by treatment with **retinoic** acid was used in this study as a **cell** culture **model** for human neuronal **cells**. The hypoxia-inducible VEGF promoter in plasmid vectors was employed to drive the expression of marker genes (luciferase) and **therapeutic** genes (bcl2) in hypoxic NT2 **cells** and NT2N neurons in culture. Cationic liposomes complexed with plasmid DNA were used for transfection of vectors with the constitutive cytomegalovirus promoter (pCMV) or the hypoxia-inducible VEGF promoter (pHRE). Hypoxic or normoxic control NT2 **cells** transfected with pCMV-luciferase showed high transgene expression (2.4 x 10(8) relative light units (RLU)/mg protein). Control NT2 **cells** transfected with pHRE-luciferase had a rather low activity (4.9 x 10(6) RLU/mg protein), which was induced 34-fold under hypoxic conditions. Four-fold induction of luciferase expression was obtained in hypoxic NT2N neurons transfected with pHRE compared with normoxic controls. The hypoxia-induced luciferase expression in NT2N **cells** was 34% of the activity of pCMV-luciferase under the same conditions. Transfection of NT2N neurons with pCMV-bcl2 or pHRE-bcl2 was demonstrated to reduce significantly the numbers of apoptotic **cells** after hypoxia. These results demonstrate efficient VEGF promoter-mediated induction of transgene expression in hypoxic human neurons. This **cell** culture **model** may be employed for the further investigation of **therapeutic** proteins against ischemic brain damage due to neuronal

leukaemia **cell** extravasation in a novel organotypic **model** for vessel wall and measured plasma ICAM-1 and -2 levels in acute leukaemia patients at diagnosis and during chemotherapy. We found that both normal mononuclear **cells** and blast **cells** from acute leukaemia patients, as well as **retinoic** acid-treated promyelocytic leukaemia **cells**, rapidly extravasated through **endothelial cell** layers into the underlying collagen matrix. ICAM-1 antibody prevented the extravasation, while antibodies to other adhesion molecules showed little (CD18, ICAM-2) or no inhibition (CD11a and ICAM-3). Soluble ICAM-1 (sICAM-1) protein had no effect. We also observed increased plasma sICAM-1 and -2 levels in leukaemia patients and found that they correlated only weakly with the white blood **cell** count. No correlation was found between sICAM-1 or -2 levels and the response to **therapy**. Although elevated sICAM-2 levels decreased rapidly during chemotherapy, sICAM-1 levels did not. Because sICAM-1 protein had no effect on leukaemia **cell** extravasation in vitro, it is probable that the increased plasma sICAM-1 levels in leukaemia patients may not play a role in leukaemia **cell** infiltration. However, as we showed that ICAM-1 mediated leukaemia **cell** extravasation on the **cell** surface, it is possible that **cellular** ICAM-1 has an important role in disease progression.

5/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11289513 21324325 PMID: 11431341
Inhibition of fibroblast growth factor-2-induced vascular tumor formation by the acyclic nucleoside phosphonate cidofovir.
Liekens S; Neyts J; De Clercq E; Verbeken E; Ribatti D; Presta M
Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium. sandra.liekens@rega.kuleuven.ac.be
Cancer research (United States) Jul 1 **2001**, 61 (13) p5057-64, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cidofovir [(S)-HPMPC; (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] is an antiviral drug that has been approved for the treatment of cytomegalovirus **retinitis** in AIDS patients. Cidofovir also possesses potent inhibitory activity against various human papillomavirus-induced tumors in animal **models** and patients. In addition, cidofovir inhibits the development of murine polyomavirus-induced hemangiomas in rats by an as-yet-uncharacterized, antivirus-independent mechanism. Here we report the inhibitory effect of cidofovir on the development of virus-independent vascular tumors originated by basic fibroblast growth factor (FGF2)-overexpressing **endothelial cells** (FGF2-T-MAE **cells**). In vitro, cidofovir was cytostatic to FGF2-T-MAE **cells** at a 50% cytostatic concentration of 6.7 microg/ml. Cidofovir concentrations >25 microg/ml resulted in cytotoxicity because of induction of apoptosis. Cidofovir did not affect FGF2-T-MAE **cell** sprouting in three-dimensional fibrin gel and morphogenesis on Matrigel at noncytotoxic concentrations. In vivo, cidofovir (100 microg/egg) completely suppressed hemangioma formation on the chick chorioallantoic membrane (CAM) induced by intra-allantoic injection of FGF2-T-MAE **cells**, without affecting the formation of normal CAM vessels. Accordingly, cidofovir applied locally at 200 microg/disc, reduced neovascularization on the CAM by only 35%. Intratumoral or systemic administration of cidofovir caused a significant inhibition of the growth of s.c., i.p., or intracerebral FGF2-T-MAE xenografts in nude mice and severe combined immunodeficient mice. Drug-induced apoptosis was observed in FGF2-T-MAE tumors as soon as 2 days after the beginning of treatment. In conclusion, cidofovir appears to inhibit the growth of endothelium-derived tumors via induction of apoptosis

Developments of these strategies are ongoing and they include identification of more potent inhibitors, antiangiogenic gene **therapy** , improvement of protein/compound half-lives in the circulation, increase of their concentrations at the disease location, and combinatorial **therapies** with approaches including chemotherapy, radiotherapy, and immunotherapy. Despite the above-mentioned disadvantages, a few inhibitors have entered into the early stages of clinical trials and they may bring new hopes for the treatment of cancer and other angiogenesis dependent diseases.

5/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11167086 21214540 PMID: 11313884
Two distinct signalling pathways are involved in FGF2-stimulated proliferation of choriocapillary **endothelial cells** : a comparative study with VEGF.
Zubilewicz A; Hecquet C; Jeanny J C; Soubrane G; Courtois Y; Mascarelli F
Medical School in Lublin, Department of Ophthalmology, ul. Chmielna 1, 20-079, Lublin, Poland.
Oncogene (England) Mar 22 **2001**, 20 (12) p1403-13, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In the **retina** , angiogenesis is an important component of normal physiological events such as embryonic vascular development. It is also involved in pathological processes including diabetic **retinopathies** and age-related macular degeneration, and tumour growth such as choroidal melanoma. Fibroblast growth factor (FGF) 2 and vascular **endothelial cell** growth factor (VEGF) are the two major angiogenic factors in the **retina** . We investigated the mechanism of proliferation and the regulation of the mitogenic properties of FGF2 and VEGF in cultures of chorocapillary **endothelial cells** (CEC). FGF2 is a strong mitogen for CEC and induced a 2.5-fold increase in **cell** proliferation after 4 days in culture in the absence of serum. In contrast, VEGF is a poor mitogen for CEC. FGF2, but not VEGF induces a large activation of MEK1, ERK1/2 and P90(RSK) during CEC proliferation. Pharmacological inhibition of Ras processing, and of MEK1 and ERK1/2 activation reduced only by 50% FGF2-induced **cell** proliferation, suggesting that there is another signalling pathway for CEC proliferation. Pharmacological inhibition of the PI 3-Kinase also inhibits by half FGF2-induced CEC proliferation. FGF2 stimulates the activation of the PI 3-K, P70(S6K) and Akt. Inhibition of both ERK1/2 and PI 3-K activities suppressed FGF2-induced CEC proliferation, demonstrating that CEC proliferation requires both ERKs and PI 3-K pathways. These data on the molecular mechanism and signalling may have important implications for providing more selective methods for anti-angiogenic and anti-tumoural **therapy**.

5/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11016065 21022433 PMID: 11141672
The status of gene **therapy** in cardiovascular medicine]
Stellenwert der Gentherapie in der kardiovaskularen Medizin.
Auer J; Berent R; Schleicher K; Eber B
II. Interne Abteilung mit Kardiologie und Internistische Intensivmedizin, Allgemeines offentliches Krankenhaus der Barmherzigen Schwestern vom Hl. Kreuz, Wels, Osterreich. johann.auer@khwels.at
Herz (Germany) Nov **2000**, 25 (7) p635-42, ISSN 0340-9937 Journal Code: 7801231

Document type: Journal Article ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed

Vascular gene transfer potentially offers new treatments for cardiovascular diseases. It may be used to overexpress **therapeutically** important proteins and correct genetic defects, and to test experimentally the effects of various genes in a local vascular compartment. Vascular **endothelial** growth factor (VEGF) and fibroblast growth factor (FGF) gene transfers have improved blood flow and collateral development in ischemic limb and myocardium. Promising **therapeutic** effects have been obtained in animal **models** of restenosis or vein-graft thickening with the transfer of genes coding for VEGF, nitric-oxide synthase, thymidine kinase, **retinoblastoma** , growth arrest homoeobox, tissue inhibitor of metalloproteinases, cyclin or cyclin-dependent kinase inhibitors, fas ligand and hirudin, and antisense oligonucleotides against transcription factors or **cell** -cycle regulatory proteins. First experiences of VEGF gene transfer and decoy oligonucleotides in human beings have been reported. However, further developments in gene transfer vectors, gene delivery techniques and identification of effective treatment genes will be required before the full **therapeutic** potential of gene **therapy** in cardiovascular disease can be assessed.

5/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10971374 20526948 PMID: 11076319

Angiogenesis and vasculogenesis. **Therapeutic** strategies for stimulation of postnatal neovascularization]

Angiogenese und Vaskulogenese. **Therapeutische** Strategien zur Stimulation der postnatalen Neovaskularisation.

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Herz (GERMANY) Sep **2000**, 25 (6) p611-22, ISSN 0340-9937
Journal Code: 7801231

Document type: Journal Article; Review; Review, Tutorial ; English Abstract
Languages: GERMAN
Main Citation Owner: NLM
Record type: Completed

The formation of new blood vessel is essential for a variety of physiological processes like embryogenesis and the female reproduction as well as wound healing and neovascularization of ischemic tissue. Major progress in understanding the underlying mechanisms regulating blood vessel growth has offered novel **therapeutic** options in the treatment of a variety of diseases including ischemic cardiovascular disorders. Vasculogenesis and angiogenesis are the mechanisms responsible for the development of the blood vessels. Angiogenesis refers to the formation of capillaries from preexisting vessels in the embryo and adult organism. While pathologic angiogenesis includes the role of post-natal neovascularization in the pathogenesis of arthritis, diabetic **retinopathy**, and tumor growth and metastasis, **therapeutic** angiogenesis, either endogenously or in response to administered growth factors, includes the development of collateral blood vessels in tissue ischemia. Preclinical studies established that angiogenic growth factors could promote collateral artery development in animal **models** of peripheral and myocardial ischemia. Subsequent clinical trials using gene transfer of naked DNA encoding for VEGF for the treatment of critical limb and myocardial ischemia documented the safety and clinical benefit of this novel **therapeutic** approach. Several objective methods indicated

marked improvement in collateral vessel development. Vasculogenesis describes the development of new blood vessels from in situ differentiating **endothelial cells** . Recently considered to be restricted to embryogenesis, there exists now striking evidence that **endothelial** progenitor **cells** (EPC) circulate also in adult peripheral blood able to participate in ongoing neovascularization. Different cytokines and growth factors have a stimulatory effect on these bone-marrow derived EPC. Granulocyte macrophage colony stimulating factor (GM-CSF) and vascular **endothelial** growth factor (VEGF) mobilize EPC from the bone marrow into the peripheral circulation. While their endogenous contribution to postnatal neovascularization needs to be documented, the iatrogenic expansion and mobilization of EPC might represent an effective means to augment the resident population of **endothelial cells** (ECs). This kind of **cell therapy** for tissue regeneration in ischemic cardiovascular diseases opens a novel and challenging clinical option besides or in addition to the use of growth factors in gene **therapy**.

5/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10930402 20496864 PMID: 11040088
Quantitative image analysis of laser-induced choroidal neovascularization in rat.
Edelman J L; Castro M R
Department of Biological Sciences, Allergan Inc., Irvine, CA, USA. edelman jeffrey@allergen.com
Experimental eye research (ENGLAND) Nov **2000**, 71 (5) p523-33, ISSN 0014-4835 Journal Code: 0370707
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Rodent **models** of laser-induced choroidal neovascularization (CNV) are now extensively used to identify angiogenic proteins, determine the role of specific genes with knockout mice, and evaluate the efficacy and safety of anti-angiogenic **therapies**. CNV is typically evaluated by fluorescein angiography or vascular **endothelial cell** labeling in histologic sections. The current study examined an alternative method using high molecular weight FITC-dextran (MW 2 x 10(6)) for high resolution angiography in RPE-choroid-sclera flat mounts. At 24 hr after lasering, the lesions appeared as a circular weakly fluorescent area of approximately equal diameter to the laser spot. No FITC-dextran labeled blood vessels were visible in the lesion at day 1. Three days after lasering, 47% of the lesions showed FITC-dextran labeling indicative of CNV. The incidence (71%) and extent of CNV increased by day 6, and by day 10 all lesions were vascularized, and the maximal area was attained. No significant change followed day 10, and the neovascular area remained constant through day 31. The highest rate of blood vessel growth (between 3 and 10 days after laser) correlates with the peak expression of VEGF, bFGF, and their receptors shown in previous studies. Morphologic analysis of flat mounts and histologic sections showed that the neovascular plexus in most lesions originates from deeper choroidal vessels in the center of the lesion, grows towards the neural **retina** , then branches circumferentially to anastamose with uninjured choriocapillaris. The microvessels in these lesions are broad and flat, similar to normal choriocapillaris. In a separate study, rats were treated daily with the angiostatic corticosteroid dexamethasone (20-500 microg kg(-1)day(-1)), and CNV was examined at day 10 in FITC-dextran labeled flat mounts and histologic sections. Dexamethasone dose-dependently inhibited CNV, and its highest dose inhibited approximately 95% of CNV labeled by FITC-dextran and resulted in lesions with no detectable Factor VIII immunostaining. High resolution angiography with FITC-dextran is reproducible and quantifiable, and it may accelerate the discovery of **therapeutic** agents that modulate choroidal

neovascularization. Copyright 2000 Academic Press.

5/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10831636 20391325 PMID: 10937546
Gene transfer of a soluble receptor of VEGF inhibits the growth of experimental eyelid malignant melanoma.
Shiose S; Sakamoto T; Yoshikawa H; Hata Y; Kawano Y; Ishibashi T; Inomata H; Takayama K; Ueno H
Department of Ophthalmology, Research Institute of Angiocardiology and Cardiovascular Clinic, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
Investigative ophthalmology & visual science (UNITED STATES) Aug **2000**, 41 (9) p2395-403, ISSN 0146-0404 Journal Code: 7703701
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To determine the effect of adenovirus-mediated gene transfer of a soluble receptor of vascular **endothelial** growth factor (VEGF) on the growth of experimental eyelid malignant melanoma. METHODS: An adenovirus vector encoding a soluble VEGF receptor/flt-1 (Adflt-ExR) was constructed. The bovine **retinal endothelial cells** (ECs) were incubated in a culture medium of 293E1 **cells** infected by means of an adenovirus vector or uninfected (control), which contained human recombinant VEGF, and the [3H]thymidine uptake was tested. The experimental eyelid malignant melanoma was induced by the injection of B16 melanoma **cells** (4 x 10(6) **cells**) into the right upper eyelid of BALB/c nu/nu mice, and the size of the tumor was recorded for 3 weeks after tumor **cell** injection. The effect of Adflt-ExR was examined in three ways. **Model** 1: B16 **cells** were infected by Adflt-ExR beforehand (at a multiplicity of infection [MOI] of 10) and injected into the eyelid. **Model** 2: Adflt-ExR was injected into pre-established B16 **cell** -induced eyelid malignant melanoma. **Model** 3: Adflt-ExR was injected into the femoral muscle of mice before B16 **cell** injection into the eyelid, and the remote effect was evaluated. An adenovirus vector bearing the LacZ gene (AdLacZ) or phosphate-buffered saline was used as a control. The amount of VEGF and the flt-ExR protein was measured by sandwich enzyme-linked immunosorbent assay (ELISA). Vascularization was evaluated by counting the number and the size of the vessels. RESULTS: The supernatant of Adflt-ExR-transfected **cells** clearly inhibited VEGF-induced bovine **retinal** EC proliferation in vitro. In **models** 1 and 2, the tumor growth in Adflt-ExR-treated mice was significantly lower than that of controls ($P < 0.05$). In **model** 3, no significant difference was found ($P = 0.14$). The molar ratio of VEGF/flt-ExR protein was clearly low in the tumors of Adflt-ExR-treated mice in **models** 1 and 2 ($P < 0.01$) but not in **model** 3 ($P > 0.05$). In vessel density, the tumors in Adflt-ExR-treated mice had fewer vessels than tumors in control animals in **models** 1 and 2 ($P < 0.05$). CONCLUSIONS: Adenovirus-mediated gene transfer of a soluble form of VEGF receptor (flt-1) gene inhibited the growth of the experimental eyelid malignant melanoma. This method may be useful as an antiangiogenic **therapy** for eyelid malignant melanoma.

5/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10820072 20368870 PMID: 10906490
Primary cultures of brain microvessel **endothelial cells**: a valid and flexible **model** to study drug transport through the blood-brain barrier in vitro.
Franke H; Galla H; Beuckmann C T

Institut fur Biochemie, Westfalische Wilhelms-Universitat Munster, Wilhelm-Klemm-Str. 2, 48149, Munster, Federal Republic of Germany.
Brain research. Brain research protocols (NETHERLANDS) Jul **2000**, 5 (3) p248-56, ISSN 1385-299X Journal Code: 9716650
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Studies on drug entry into the brain and permeation of the blood-brain barrier start to gain more and more importance in neuropharmaceutical research in order to develop new drugs for the **therapy** of central nervous system diseases. Procedures that provide quick access to permeation properties of those drugs with high throughput are difficult to achieve with animal **models**. Although various useful **cell** culture **models** approaching this issue have been described, results are often not comparable among each other unless determined with an equal experimental setup. Reproducibility of **cell** culture methods as well as corresponding findings gathered with these tools are often impeded due to the lack of details in experimental manuals. Here we present a precise manual for preparation and maintenance of porcine brain microvessel **endothelial cells**, serving as a culture **model** of the blood-brain barrier. Furthermore experimental details for blood-brain barrier transport investigations are presented. Validation of this **model** was carried out by determination of bioelectric properties and permeation experiments using various marker molecules reflecting paracellular and transcellular blood-brain barrier penetration. Results obtained with our **model** are closely resembling the in vivo-situation although astrocytes are not included. This simplification of the system is one of the major advantages towards robot derived **cell** cultures necessary for high throughput screening.

5/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10819403 20377770 PMID: 10917997
Opioid growth factor modulates angiogenesis.
Blebea J; Mazo J E; Kihara T K; Vu J H; McLaughlin P J; Atnip R G; Zagon I S
Department of Surgery and the Department of Neuroscience and Anatomy, The Pennsylvania State University College of Medicine, Hershey, PA, USA.
Journal of vascular surgery : official publication, the Society for Vascular Surgery and International Society for Cardiovascular Surgery, North American Chapter (UNITED STATES) Aug **2000**, 32 (2) p364-73, ISSN 0741-5214 Journal Code: 8407742
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: Induced angiogenesis has recently been attempted as a **therapeutic** modality in patients with occlusive arterial atherosclerotic disease. We investigated the possible role of endogenous opioids in the modulation of angiogenesis. METHODS: Chick chorioallantoic membrane was used as an in vivo **model** to study angiogenesis. Fertilized chick eggs were incubated for 3 days, explanted, and incubated for an additional 2 days. Three-millimeter methylcellulose disks were placed on the surface of the chorioallantoic membrane; each disk contained opioid growth factor ([Met(5)]-enkephalin; 5 microgram), the short-acting opioid receptor antagonist naloxone (5 microgram), opioid growth factor and naloxone together (5 microgram of each), the long-acting opioid antagonist naltrexone (5 microgram), or distilled water (control). A second series of experiments was performed with distilled water, the angiogenic inhibitor **retinoic** acid (1 microgram), and vascular **endothelial** growth factor (1 microgram) to further evaluate our **model**. The developing

vasculature was imaged 2 days later with a digital camera and exported to a computer for image analysis. Total number of blood vessels, total vessel length, and mean vessel length were measured within a 100-mm(2) region surrounding each applied disk. Immunocytochemical analysis was performed with antibodies directed against opioid growth factor and its receptor (OGFr). RESULTS: Opioid growth factor had a significant inhibitory effect on angiogenesis, both the number of blood vessels and the total vessel length being decreased (by 35% and 20%, respectively) in comparison with control levels (P <.005). The simultaneous addition of naloxone and opioid growth factor had no effect on blood vessel growth, nor did naloxone alone. Chorioallantoic membranes exposed to naltrexone displayed increases of 51% and 24% in blood vessel number and length, respectively, in comparison with control specimens (P <.005). These results indicate that the opioid growth factor effects are receptor mediated and tonically active. Immunocytochemistry demonstrated the presence of both opioid growth factor and OGFr within the **endothelial cells** and mesenchymal **cells** of the developing chorioallantoic membrane vessel wall. **Retinoic** acid significantly reduced the number and the total length of blood vessels, whereas vascular **endothelial** growth factor increased both the number and the length of blood vessels in comparison with the controls (P <.0001). The magnitude of opioid growth factor's effects were comparable to those seen with **retinoic** acid, whereas inhibition of opioid growth factor with naltrexone induced an increase in total vessel length comparable to that for vascular **endothelial** growth factor. CONCLUSIONS: These results demonstrate for the first time that endogenous opioids modulate in vivo angiogenesis. Opioid growth factor is a tonically active peptide that has a receptor-mediated action in regulating angiogenesis in developing **endothelial** and mesenchymal vascular **cells**.

5/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10804602 20349651 PMID: 10889114
The possibility of gene **therapy** for the treatment of choroidal neovascularization.
Murata T; Cui J; Taba K E; Oh J Y; Spee C; Hinton D R; Ryan S J
Doheny Eye Institute and Department of Ophthalmology, Keck School of Medicine of the University of Southern California, Los Angeles, California 90033, USA.
Ophthalmology (UNITED STATES) Jul **2000**, 107 (7) p1364-73, ISSN 0161-6420 Journal Code: 7802443
Contract/Grant No.: EY015245; EY; NEI; EY03040; EY; NEI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Choroidal neovascularization (CNV) is responsible for most cases of severe visual loss in age-related macular degeneration. Recently, the possibility of gene **therapy** has been proposed for the treatment of CNV. The purpose of this study was to examine the feasibility of ex vivo and in situ gene **therapy** approaches for CNV. DESIGN: Experimental study. METHODS: Human **retinal** pigment epithelial (RPE) **cells** were transduced with a retroviral vector coding for beta-galactosidase. Transduced **cells** were grown on type II collagen sheets and transplanted under the **retina** of 20 rabbits. Animals were observed for 3 to 56 days, and transplanted **cells** were examined histologically and with X-gal staining. Bovine choroidal **endothelial cells** (CEC) were transduced with retroviral vectors coding for tissue inhibitor of metalloproteinase-2 (TIMP-2) or control vector. Production of TIMP-2 by transduced **cells** was determined by immunohistochemical analysis and enzyme-linked immunosorbent assay. Effect of transduction on in vitro proliferation, migration, and tube formation was examined in response to

vascular **endothelial** growth factor (VEGF). Four CNV lesions were induced in one cynomolgus monkey by laser photocoagulation. Two days later, retroviral vector coding for TIMP-2 or control vector was injected into the subretinal space overlying the CNV lesions. The monkey was observed for 12 weeks using fluorescein angiography. RESULTS: Transplantation of transduced RPE **cells** was technically achieved in 10 of 20 animals. In these animals, RPE **cells** at the site of transplantation formed a monolayer and expressed beta-galactosidase for 14 days. beta-Galactosidase-positive **cells** were not identified at 56 days. Choroidal **endothelial cells** transduced with TIMP-2 secrete TIMP-2 into the media and show decreased migration and tube formation in vitro. In the in vivo monkey **model** , the control CNV lesions (n = 2) showed prominent leakage, whereas the experimental lesions (n = 2) showed minimal hyperfluorescence. CONCLUSIONS: Retrovirally transduced RPE **cells** survive in the subretinal space for at least 14 days and continue to express the gene product coded for by the vector. Choroidal **endothelial cells** retrovirally transduced for TIMP-2 produce TIMP-2 in vitro and show decreased angiogenic responses in vitro in response to VEGF. A preliminary study attempting in situ delivery of TIMP-2 vector to CNV lesions in a monkey eye supports the feasibility of this approach and encourages further study.

5/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10777745 20343946 PMID: 10888033
PKC412--a protein kinase inhibitor with a broad **therapeutic** potential.
Fabbro D; Ruetz S; Bodis S; Pruschy M; Csermak K; Man A; Campochiaro P; Wood J; O'Reilly T; Meyer T
Novartis Pharma Inc., Department of Oncology Research and Clinical Oncology, Basel, Switzerland. doriano.fabbro@pharma.novartis.com
Anti-cancer drug design (ENGLAND) Feb **2000**, 15 (1) p17-28, ISSN 0266-9536 Journal Code: 8603523
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The staurosporine derivative PKC412 was originally identified as an inhibitor of protein kinase C (PKC) and subsequently shown to inhibit other kinases including the kinase insert domain receptor (KDR) (vascular **endothelial** growth factor receptor, VEGF-R2), the receptor of platelet-derived growth factor, and the receptor for the stem **cell** factor, c-kit. PKC412 showed a broad antiproliferative activity against various tumor and normal **cell** lines in vitro, and was able to reverse the Pgp-mediated multidrug resistance of tumor **cells** in vitro. Exposure of **cells** to PKC412 resulted in a dose-dependent increase in the G2/M phase of the **cell** cycle concomitant with increased polyploidy, apoptosis and enhanced sensitivity to ionizing radiation. PKC412 displayed a potent antitumor activity as single agent and was able to potentiate the antitumor activity of some of the clinically used cytotoxins (Taxol and doxorubicin) in vivo. The combined treatment of PKC412 with loco-regional ionizing irradiation showed significant antitumor activity against tumors which are resistant to both ionizing radiation and chemotherapeutic agents (dysfunctional p53). The finding that PKC412 is an inhibitor of the VEGF-mediated **cellular** signaling via inhibition of KDR and PKC in vitro is consistent with the in vivo inhibition of VEGF-dependent angiogenesis in a growth factor implant **model**. Orally administered PKC412 also strongly inhibited **retinal** neovascularization as well as laser-induced choroidal neovascularization in murine **models** . In summary, PKC412 may suppress tumor growth by inhibiting tumor angiogenesis in addition to directly-inhibiting tumor **cell** proliferation via its effects on PKC and/or other protein

kinases. PKC412 is currently in Phase I clinical trials for treatment of advanced cancer as well as for the treatment of ischemic **retinopathy**.

5/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10610998 20137598 PMID: 10675133
Cardiovascular gene **therapy**.
Yla-Herttuala S; Martin J F
A I Virtanen Institute and Department of Medicine, University of Kuopio, Finland. Seppo.YlaHerttuala@uku.fi
Lancet (ENGLAND) Jan 15 **2000**, 355 (9199) p213-22, ISSN 0140-6736 Journal Code: 2985213R
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Vascular gene transfer potentially offers new treatments for cardiovascular diseases. It can be used to overexpress **therapeutically** important proteins and correct genetic defects, and to test experimentally the effects of various genes in a local vascular compartment. Vascular **endothelial** growth factor (VEGF) and fibroblast growth factor (FGF) gene transfers have improved blood flow and collateral development in ischaemic limb and myocardium. Promising **therapeutic** effects have been obtained in animal **models** of restenosis or vein-graft thickening with the transfer of genes coding for VEGF, nitric-oxide synthase, thymidine kinase, **retinoblastoma** , growth arrest homoeobox, tissue inhibitor of metalloproteinases, cyclin or cyclin-dependent kinase inhibitors, fas ligand and hirudin, and antisense oligonucleotides against transcription factors or **cell** -cycle regulatory proteins. First experiences of VEGF gene transfer and decoy oligonucleotides in human beings have been reported. However, further developments in gene-transfer vectors, gene-delivery techniques and identification of effective treatment genes will be required before the full **therapeutic** potential of gene **therapy** in cardiovascular disease can be assessed.

5/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10605191 20143040 PMID: 10680847
Anti-human immunodeficiency virus type 1 gene **therapy** in human central nervous system-based **cells** : an initial approach against a potential viral reservoir.
Mukhtar M; Duke H; BouHamdan M; Pomerantz R J
Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA.
Human gene therapy (UNITED STATES) Jan 20 **2000**, 11 (2) p347-59 , ISSN 1043-0342 Journal Code: 9008950
Contract/Grant No.: MH58526; MH; NIMH
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Studies have demonstrated that human immunodeficiency virus type 1 (HIV-1) infection of central nervous system (CNS)-based **cells** in vivo results in a series of devastating clinical conditions collectively termed acquired immune deficiency syndrome (AIDS) dementia complex (ADC). Gene **therapy** for these neurovirological disorders necessitates utilization of a vector system that can mediate in vivo delivery and long-term expression of an antiretroviral transgene in nondividing/postmitotic CNS **cellular** elements. The present studies focus on the transfer of an

anti-HIV-1 gene to primary isolated CNS microvascular **endothelial cells** (MVECs) and neuronal-based **cells** , for its effects in protecting these **cells** from HIV-1 infection. By using an HIV-1-based vector system, it was possible to efficiently transduce and maintain expression of a marker transgene, beta-galactosidase (beta-Gal), in human CNS MVECs, human fetal astrocytes, plus immature and mature (differentiated) NT2 **cells** . Significant transduction of the marker gene, beta-Gal, in CNS-based **cells** prompted the utilization of this system with an anti-HIV-1 gene **therapeutic** construct, RevM10, a trans-dominant negative mutant Rev protein. Initially, it was not possible to generate any HIV-1 vector particles with the RevM10 gene in the transducing construct, because of inhibitory effects on the HIV-1 vector by this gene product. However, the vector could be partially rescued by adding an additional construct that supplied wild-type rev, in trans, during a multiple construct transfection in the packaging 293T **cells**. Thus, it was possible to significantly improve the titer of RevM10-expressing viral particles generated from these **cells**. Moreover, this RevM10 vector transduced the neuronal precursor **cell** line NT2, **retinoic** acid-differentiated human neurons (hNT) from the precursor **cells**, and primary isolated human brain MVECs with high efficiency. RevM10 generated from the HIV-1-based vector system potently inhibited replication of diverse HIV-1 strains in human CNS MVECs and neuronal **cells**. The data generated from these studies represent an initial approach for future development of anti-HIV-1 gene **therapy** in the CNS.

5/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10580121 20107906 PMID: 10643294
Cell biology of intraocular vascular diseases]
Ishibashi T
Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University.
Nippon Ganka Gakkai zasshi (JAPAN) Dec **1999**, 103 (12) p923-47, ISSN 0029-0203 Journal Code: 7505716
Document type: Journal Article; Review; Review Literature ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed
Diabetic **retinopathy** (DR) still remains the leading cause of blindness in the working population of Japan and western world, though **therapies** such as **retinal** photocoagulation and vitrectomy can be remarkably effective when administered at an appropriate stage in the disease process. Consequently, there is a need for further investigation of the pathogenesis of DR to develop better **therapy**. DR is characterized by gradually progressive alterations in the **retinal** microvasculature, leading to three fundamental morbidities: 1. vascular hyperpermeability, 2. vascular occlusion, and 3. neovascularization. Recent studies have revealed that hyperglycemia causes several metabolic disorders which cause DR directly or indirectly through the abnormal expression of cytokines including vascular **endothelial** growth factor (VEGF). In this study, we performed precise tests of the correlation between intraocular VEGF and the three fundamental changes in the diabetic **retina** mentioned above. Ultrastructural study of the human **retina** revealed that two major pathways are responsible for hyperpermeability of diabetic **retinal** vessels, i.e., intercellular or paracellular transport (opening of the tight junctions) and intracellular or transcellular transport (caveolae, intracytoplasmic vesicles, and fenestration). All these pathways were induced by intravitreal injection of VEGF. The major trigger of VEGF overexpression is tissue ischemia caused by vascular occlusion. However, the **retinas** from the eyes with background DR revealed increased expression of VEGF without apparent incidence of vascular occlusion. We

have identified accumulation of advanced glycation end products (AGEs) in these **retinas** , and found that AGEs are a major stimulus for VEGF overexpression in background DR. **Retinal** vascular occlusion was caused by thrombus formation primarily in the capillary vessels. Thrombi mainly consisted of fibrin, platelets, and leucocytes in the early stage of their formation, and glial **cells** and macrophages were also involved in the later stage. The blood coagulation process plays an important role in fibrin formation in thrombi. The expression of tissue factor (TF), an initiator of extrinsic blood coagulation, was upregulated by VEGF in **retinal** vascular **endothelial cells** (REC). In addition, AGEs were also thrombogenic through the induction of TF expression and suppression of the expression of prostacyclin stimulating factor (PSF), which stimulate prostacyclin synthesis in vascular **endothelial cells** . These findings suggest that AGEs, VEGF, and TF could interact in a vicious circle because AGEs and VEGF could induce **retinal** vascular occlusion which results in further increase in VEGF expression. Intravitreal injection of VEGF could induce **retinal** neovascularization. VEGF stimulates vascular **endothelial cell** proliferation by binding to a specific receptor named kinase insert domain-containing receptor/fetal liver kinase (KDR/Flk-1, KDR). AGEs and basic fibroblast growth factor (bFGF) induced expression of KDR in REC, and a transcription factor Sp 1 was involved in this process. Since the expression of KDR as well as VEGF was already upregulated in the **retinas** with background DR, VEGF appeared to start to induce the proliferative changes long before the actual onset of proliferative DR. These findings indicated that VEGF and its receptor system plays a pivotal role all through the disease process of DR. We considered that amelioration of the activated VEGF and its receptor system could lead to the development of new **therapy** for DR. We have developed two novel methods to prevent **retinal** neovascularization by inhibiting VEGF and its receptor system. 1. An insulin sensitizing agent (troglitazone) inhibited proliferation, migration, and in vitro tube formation by REC as well as oxygen-induced **retinal** neovascularization in a mouse **model**. Thus, glycemic control by troglitazone could reduce the incidence of neovascularization in diabetic eyes. 2. (ABSTRACT TRUNCATED)

5/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10517756 20040164 PMID: 10571534
Adenoviral RB2/p130 gene transfer inhibits smooth muscle **cell** proliferation and prevents restenosis after angioplasty.
Claudio P P; Fratta L; Farina F; Howard C M; Stassi G; Numata S; Pacilio C; Davis A; Lavitrano M; Volpe M; Wilson J M; Trimarco B; Giordano A; Condorelli G
Department of Pathology Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA. pclaudio@lac.jci.tju.edu
Circulation research (UNITED STATES) Nov 26 **1999**, 85 (11) p1032-9, ISSN 0009-7330 Journal Code: 0047103
Contract/Grant No.: PO1-NS-36466; NS; NINDS; RO1-CA-60999-01A1; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Smooth muscle **cell** (SMC) proliferation that results in neointima formation is implicated in the pathogenesis of atherosclerotic plaques and accounts for the high rates of restenosis that occur after percutaneous transluminal coronary angioplasty, a widespread treatment for coronary artery disease. **Endothelial** lesions trigger intense proliferative signals to the SMCs of the subintima, stimulating their reentry into the **cell** cycle from a resting G(0) state, resulting in neointima formation and vascular occlusion. **Cellular** proliferation is negatively controlled by growth-regulatory or tumor-suppressor genes, or

both, such as the **retinoblastoma** gene family members (RB/p105, p107, RB2/p130). In the present study, we show that RB2/p130 inhibited SMC proliferation in vitro and in vivo. We used the rat carotid artery **model** of restenosis to demonstrate that adenovirus-mediated localized arterial transduction of RB2/p130 at the time of angioplasty significantly reduced neointimal hyperplasia and prevented restenosis. Furthermore, the ability of pRb2/p130 to block proliferation correlated with its ability to bind and sequester the E2F family of transcription factors, which are important mediators of **cell** cycle progression. These results imply that RB2/p130 could be an important target for vascular gene **therapy**.

5/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10446948 99436832 PMID: 10506944
Intraocular neovascularization.
Yoshida A; Yoshida S; Ishibashi T; Inomata H
Department of Ophthalmology, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
Histology and histopathology (SPAIN) Oct **1999**, 14 (4) p1287-94 , ISSN 0213-3911 Journal Code: 8609357
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
An important character of the eye is transparency, so intraocular neovascularization, which is fragile and likely to result in hemorrhage, would cause a functional disorder of the eye and contribute to loss of vision associated with such diseases as **retinopathy** of prematurity, diabetic **retinopathy**, **retinal** vein occlusion, and age-related macular degeneration. Recently interest in the mechanisms of intraocular neovascularization has increased, and the mechanisms have been gradually elucidated using several in vitro and in vivo angiogenesis **models**. Blood vessels in the eye are composed of, and surrounded by, various types of **cells** that produce multiple factors. Neovascularization is regulated by complex interactions among these angiogenic factors, angiostatic factors, and adhesion molecules, and some of these angiogenesis-related molecules have also been suggested as new targets for novel **therapeutic** agents of intraocular neo-vascularization. This review focuses on in vivo representative angiogenesis **models** of the corneal pocket **model** and the **model** of oxygen-induced **retinopathy** , and discusses the role of some angiogenesis-related factors and adhesion molecules in intraocular neovascularization.

5/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10429890 99422990 PMID: 10494799
Molecular and biological properties of vascular **endothelial** growth factor.
Ferrara N
Department of Cardiovascular Research, Genentech Inc., South San Francisco, CA 94080, USA. nf@gene.com
Journal of molecular medicine (Berlin, Germany) (GERMANY) Jul **1999**, 77 (7) p527-43, ISSN 0946-2716 Journal Code: 9504370
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Vascular **endothelial** growth factor (VEGF) is a fundamental regulator of normal and abnormal angiogenesis. Recent evidence indicates that VEGF is essential for embryonic vasculogenesis and angiogenesis.

Furthermore, VEGF is required for the cyclical blood vessel proliferation in the female reproductive tract and for longitudinal bone growth and endochondral bone formation. Substantial experimental evidence also implicates VEGF in pathological angiogenesis. Anti-VEGF monoclonal antibodies or other VEGF inhibitors block the growth of many tumor **cell** lines in nude mice. Furthermore, the concentrations of VEGF are elevated in the aqueous and vitreous humors of patients with proliferative **retinopathies** such as the diabetic **retinopathy**. In addition, VEGF-induced angiogenesis results in a **therapeutic** benefit in several animal **models** of myocardial or limb ischemia. Currently, both **therapeutic** angiogenesis using recombinant VEGF or VEGF gene transfer and inhibition of VEGF-mediated pathological angiogenesis are being pursued.

5/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10413155 99398511 PMID: 10469350
Role of vascular **endothelial** growth factor in the regulation of angiogenesis.
Ferrara N
Department of Cardiovascular Research, Genentech, Inc., South San Francisco, California 94080, USA. nf@gene.com
Kidney international (UNITED STATES) Sep **1999**, 56 (3) p794-814
, ISSN 0085-2538 Journal Code: 0323470
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Compelling evidence indicates that vascular **endothelial** growth factor (VEGF) is a fundamental regulator of normal and abnormal angiogenesis. The loss of a single VEGF allele results in defective vascularization and early embryonic lethality. VEGF plays also a critical role in kidney development, and its inactivation during early postnatal life results in the suppression of glomerular development and kidney failure. Recent evidence indicates that VEGF is also essential for angiogenesis in the female reproductive tract and for morphogenesis of the epiphyseal growth plate and endochondral bone formation. Substantial experimental evidence also implicates VEGF in pathological angiogenesis. Anti-VEGF monoclonal antibodies or other VEGF inhibitors block the growth of several human tumor **cell** lines in nude mice. Furthermore, the concentrations of VEGF are elevated in the aqueous and vitreous humors of patients with proliferative **retinopathies** such as the diabetic **retinopathy**. In addition, VEGF-induced angiogenesis results in a **therapeutic** benefit in several animal **models** of myocardial or limb ischemia. Currently, both **therapeutic** angiogenesis using recombinant VEGF or VEGF gene transfer and inhibition of VEGF-mediated pathological angiogenesis are being pursued clinically.

5/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10403488 99410964 PMID: 10481350
[Ginkgo biloba extract (EGb 761). State of knowledge in the dawn of the year 2000]
Extrait de Ginkgo biloba (EGb 761). Etat des connaissances a l'aube de l'an 2000.
Clostre F
Institut Henri Beaufour, Les Ulis.
Annales pharmaceutiques francaises (FRANCE) Jul **1999**, 57 Suppl 1
p1S8-88, ISSN 0003-4509 Journal Code: 2985176R
Document type: Journal Article; Review; Review, Academic ; English

Abstract

Languages: FRENCH

Main Citation Owner: NLM

Record type: Completed

EGb 761 is a standardized extract of dried leaves of Ginkgo biloba containing 24% ginkgo-flavonol glycosides, 6% terpene lactones such as ginkgolides A, B, C, J and bilobalide. Its broad spectrum of pharmacological activities allows it to be in adequacy to the numerous pathological requirements--hemodynamic, hemorheological, metabolic--which occur in cerebral, **retinal**, cochleovestibular, cardiac or peripheral ischemia. Moreover, EGb 761 has direct effects against necrosis and apoptosis of neurons and improves neural plasticity as evidenced in vestibular compensation. At the molecular and the **cellular** levels, some evidence obtained with animal **models** indicates that EGb 761 can interact as a free radical-scavenger and a inhibitor of lipid peroxidation with all, or nearly all reactive oxygen species; maintains ATP content by a protection of mitochondrial respiration and preservation of oxidative phosphorylations; exerts arterial and venous vasoregulator effects involving the release of **endothelial** factors and the catecholaminergic system. Moreover, EGb 761 regulates ionic balance in damaged **cells** and exerts a specific and potent Platelet-activating factor antagonist activity. Numerous well-controlled clinical studies, realized in Europe and in USA, have revealed that EGb 761 is an effective **therapy** for a wide variety of disturbances of cerebral function, ranging from cerebral impairment of ischemic vascular origins (i.e. multi infarct dementia), early cognitive decline to mild-to-moderate cases of the more severe types of senile dementias (including Alzheimer's disease) or mixed origins (i.e. psychoorganic origin). Improvement of signs and symptoms have been demonstrated for cognitive functions, particularly for memory loss, attention, alertness, vigilance, arousal and mental fluidity. Some clinical studies have showed that EGb 761 treatment may improve the capacity of geriatric patients to cope with the stressful demands of daily life. The explanation is a dual stress-alleviating action of EGb 761: its facilitates behavioral adaptation to stress and may decrease the excess of cortisol release to stress. Moreover, EGb 761 shows a specific neuroprotective effects to hippocampic **cells**. Regarding the visual system, experimental studies have shown that EGb 761 can inhibit or reduce the functional **retinal** impairments resulting from ischemia-reperfusion, photo-degeneration, diabetic or proliferative **retinopathy** . Clinical studies have revealed that EGb 761 may be useful in treating visual activity impairments and damages to the visual field associated with chronic cerebrovascular insufficiency, senile macular degeneration and diabete mellitus. Regarding the vestibular and auditory systems, experimental and clinical studies have shown the efficacy of EGb 761 in treating hypoacusis, tinnitus, vertigo, dizziness and other symptoms of vestibulocochlear disorders. At least, adequatly controlled studies in patients with peripheral arterial occlusive disease have provided good evidence for **therapeutic** efficacy in intermittent claudication. The future of EGb 761 is undoubtedly in the promise in slowing the progression of Alzheimer's disease. Indeed, two recent american clinical studies have shown the efficacy and safety of EGb 761 in patients with mild to severe Alzheimer's disease and multi-infarct dementia. In clinical terms, progression of symptoms was delayed by approximately 6 months. Actually new clinical studies are undertaken in USA and Europe. At the dawn of the third millenium (the Sixth for Ginkgo biloba) we propose a state of art about it.

5/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10279131 99285867 PMID: 10359334

Inhibitory effect of TNP-470 on experimental choroidal neovascularization in a rat **model**.

Ishida K; Yoshimura N; Mandai M; Honda Y

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Japan.

Investigative ophthalmology & visual science (UNITED STATES) Jun **1999**, 40 (7) p1512-9, ISSN 0146-0404 Journal Code: 7703701

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

PURPOSE: To determine whether an angiogenic inhibitor, TNP- 470 (TNP), an analogue of fumagillin, inhibits choroidal neovascularization (CNV) induced by diode laser photocoagulation in a rat experimental **model**. METHODS: Fundus laser photocoagulation was performed on Brown Norway rats to induce CNV. In the treatment group, TNP was administered intraperitoneally at the time of laser photocoagulation and on day 7 (50 mg/kg at each time). The incidence of CNV formation was evaluated by fluorescein angiography. The **retina** was collected from the rats on days 1, 3, 7, and 14 after laser photocoagulation, and semiquantitative polymerase chain reaction (PCR) analyses for the expression of mRNA of basic fibroblast growth factor (bFGF) and vascular **endothelial** growth factor (VEGF) were carried out. Localization of bFGF mRNA was studied by in situ reverse transcription-PCR (RT-PCR). The numbers of positively labeled **cells** for bFGF mRNA were compared between the TNP treatment and control groups. RESULTS: The incidence of CNV formation was 22.7% in the TNP-treated rats and that in the control rats was 61.4% ($P < 0.001$). The semiquantitative PCR analyses showed that bFGF mRNA was upregulated on days 3 and 7 in the control rats, but no significant changes were found in TNP-treated rats. There was no detectable difference in VEGF gene expression between the control and TNP-treated rats. bFGF mRNA was detected by in situ RT-PCR in the regenerated **retinal** pigment epithelial **cells** and **cells** of the outer and inner nuclear layers of the control rats. The number of positive **cells** for bFGF mRNA in the TNP treatment group was significantly smaller than that of the control group ($P < 0.05$) on days 3 and 14. CONCLUSIONS: TNP- 470 treatment reduced the incidence of laser-induced CNV formation in this experimental **model** . The expression of bFGF associated with CNV formation was also significantly reduced by the TNP treatment.

5/3,AB/51 (Item 51 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10220339 99197297 PMID: 10368301

Crystal structure of the kinase domain of human vascular **endothelial** growth factor receptor 2: a key enzyme in angiogenesis.

McTigue M A; Wickersham J A; Pinko C; Showalter R E; Parast C V; Tempczyk-Russell A; Gehring M R; Mroczkowski B; Kan C C; Villafranca J E; Appelt K

Agouron Pharmaceuticals, 3565 General Atomics Court, San Diego, CA 92121, USA. mctigue@agouron.com

Structure with Folding & design (UNKNOWN) Mar 15 **1999**, 7 (3) p319-30, Journal Code: 100889329

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Angiogenesis is involved in tumor growth, macular degeneration, **retinopathy** and other diseases. Vascular **endothelial** growth factor (VEGF) stimulates angiogenesis by binding to specific receptors (VEGFRs) on the surface of vascular **endothelial** **cells** . VEGFRs are receptor tyrosine kinases that, like the platelet-derived growth factor receptors (PDGFRs), contain a large insert within the kinase domain. RESULTS: We report here the generation, kinetic characterization, and 2.4 A crystal structure of the catalytic kinase domain of VEGF receptor 2 (VEGFR2). This protein construct, which lacks 50

central residues of the 68-residue kinase insert domain (KID), has comparable kinase activity to constructs containing the entire KID. The crystal structure, determined in an unliganded phosphorylated state, reveals an overall fold and catalytic residue positions similar to those observed in other tyrosine-kinase structures. The kinase activation loop, autophosphorylated on Y1059 prior to crystallization, is mostly disordered; however, a portion of it occupies a position inhibitory to substrate binding. The ends of the KID form a beta-like structure, not observed in other known tyrosine kinase structures, that packs near to the kinase C terminus. CONCLUSIONS: The majority of the VEGFR2 KID residues are not necessary for kinase activity. The unique structure observed for the ends of the KID may also occur in other PDGFR family members and may serve to properly orient the KID for signal transduction. This VEGFR2 kinase structure provides a target for design of selective anti-angiogenic **therapeutic** agents.

5/3,AB/52 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13761164 BIOSIS NO.: 200200389985
Expression profile of 11 proteins and their prognostic significance in patients with chronic lymphocytic leukemia (CLL).
AUTHOR: Faderl S; Keating M J; Do K-A; Liang S-Y; Kantarjian H M; O'Brien S ; Garcia-Manero G; Manshouri T; Albitar M(a)
AUTHOR ADDRESS: (a)Department of Laboratory Medicine, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Blvd, Box 72, Houston, TX, 77030 **USA
JOURNAL: Leukemia (Basingstoke) 16 (6):p1045-1052 June, **2002**
MEDIUM: print
ISSN: 0887-6924
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: It has been suggested that the expansion of the leukemic **cells** in chronic lymphocytic leukemia (CLL) is due to dysregulation of pathways of programmed **cell** death (apoptosis) rather than **cell** proliferation, although differences may exist in early vs late and treated vs untreated patients. In the present study, we analyzed the expression of 11 proteins in CLL **cells** that are implicated in the control of apoptosis, proliferation, and differentiation, and correlated this expression profile with survival. Using a quantitative solid-phase radioimmunoassay (RIA), we measured the **cellular** protein levels of Bcl-2, cyclin D1, PCNA, ATM, Fas, Bax, **retinoic** acid receptor alpha (RARalpha), **retinoic** acid receptor beta (RXRbeta), Flt1, VEGF, and **cellular** beta2-microglobulin in 230 samples of CLL. Univariate analysis using the Cox proportional hazard **model** showed a correlation with survival of only the following proteins: Bcl-2 ($P<0.001$), cyclin D1 ($P=0.027$), Fas ($P=0.055$), PCNA ($P<0.001$), and ATM ($P=0.028$). In a multivariate analysis using classification and regression tree analysis (CART), five groups of patients (nodes) could be generated with significant differences of survival expectation ($P<0.0001$) based on levels of expression of the above proteins. Based on CART analysis, Bcl-2 levels emerge as the most important protein in predicting survival between all 11 proteins studied. Patients with marked elevation in Bcl-2 levels had the worst outcome while patients with intermediate levels, but with high levels of PCNA and cyclin D1 or abnormal ATM expression had intermediate survival. These data indicate that intracellular levels of proteins such as Bcl-2, ATM, cyclin D1, and PCNA can be used as markers to predict clinical behavior and survival in patients with CLL. The pathways in which these proteins are involved may also represent possible targets for future **therapeutic** trials in CLL.

2002

5/3,AB/53 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13731574 BIOSIS NO.: 200200360395
Corticotropin-releasing factor receptor 2 is a tonic suppressor of vascularization.
AUTHOR: Bale Tracy L; Giordano Frank J; Hickey Reed P; Huang Yan; Nath Anjali K; Peterson Kirk L; Vale Wylie W; Lee Kuo-Fen(a)
AUTHOR ADDRESS: (a)Clayton Foundation Laboratories for Peptide Biology, The Salk Institute, 10010 N. Torrey Pines Rd., La Jolla, CA, 92037**USA
E-Mail: klee@salk.edu
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 99 (11):p7734-7739 May 28, **2002**
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Angiogenesis is regulated by means of a balance between activators and inhibitors. However, little is known regarding the regulation of the quiescent state of adult vessels. Corticotropin-releasing factor receptor 2 (CRFR2) is found in both **endothelial** and smooth muscle **cells** (SMCs) in the vasculature, where its function has remained elusive. We have investigated the role of CRFR2 as a determinant of tissue vascularization by comparing control and CRFR2-deficient mice with immunohistological and morphometric techniques. To define the mechanisms responsible for CRFR2 inhibition of angiogenesis, we have also examined in vitro the effect of ligand activation on **cell** proliferation, **cell** cycle protein phosphorylation, and capillary tube formation. Our results demonstrate that mice deficient for CRFR2 become hypervascularized postnatally. Activation of this receptor in vitro results in reduced vascular **endothelial** growth factor (VEGF) release from SMCs, an inhibition of SMC proliferation, and inhibition of capillary tube formation in collagen gels. Treatment of a subcutaneously injected gel matrix with a CRFR2 agonist inhibits growth factor-induced vascularization. Western blots show that **cell** cycle **retinoblastoma** protein, which is essential for **cell** cycle progression, is decreased by CRFR2 agonist treatment in SMCs. These results suggest that CRFR2 is a critical component of a pathway necessary for tonic inhibition of adult neovascularization. CRFR2 may be a potential target for **therapeutic** modulation of angiogenesis in cancer and ischemic cardiovascular disease.

2002

5/3,AB/54 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13684526 BIOSIS NO.: 200200313347
Morphine mimics VEGF in vascular endothelium, by promoting pro-angiogenic and survival promoting signalling and angiogenesis.
AUTHOR: Gupta Kalpna(a); Kshirsagar Smita; Chang Liming(a); Schwartz Robert ; Yee Doug(a); Law Ping-Y; Hebbel Robert P(a)
AUTHOR ADDRESS: (a)Medicine-HOT, Univ of Minnesota, 420 Delaware St SE, Minneapolis, MN, 55455**USA
JOURNAL: FASEB Journal 16 (4):pA207 March 20, **2002**

MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Morphine is used in medical conditions where blood vessels play a critical role. Morphine stimulates NO production in endothelium and activates, MAPK/ERK and proliferation in other **cells**. We hypothesized that morphine mimics VEGF signaling in endothelium and promotes angiogenesis. Morphine, and mu, delta and kappa receptor agonists stimulate human microvascular **endothelial cell** (HMEC) proliferation to the same extent as VEGF and activate MAPK/ERK and Akt, phosphorylation. These effects were abrogated by Pertussis toxin (Gi/Go Protein inhibitor) and L-NAME (NOS inhibitor). Morphine prevented apoptosis in serum starved HMEC by apprxeq35% and preserved a significantly higher number of **cells** in 'S' phase ($p<0.01$, vs untreated). Morphine induced HMEC tube formation on Matrigel (45+-15%) in vitro. In mice, Matrigel implants containing 10 muM morphine or 10 mug/ml VEGF showed higher number of blood vessels as compared to controls ($p<0.05$ & 0.001, for morphine and VEGF, respectively). Morphine administered to mice (in a dose similar to that used in cancer patients) promoted tumor angiogenesis and tumor growth in mice as compared to controls in MCF7 breast tumor xenograft **model**. Importantly, naloxone, an opiate receptor antagonist inhibited tumor progression. Given the critical role of angiogenesis in many diseases, these opioid effects could be either **therapeutically** beneficial (cardiovascular-remodelling and wound healing) or deleterious (cancer or neovascularizing **retinopathy**).

2002

5/3,AB/55 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13673673 BIOSIS NO.: 200200302494
A biodegradable injectable implant sustains systemic and ocular delivery of an aldose reductase inhibitor and ameliorates biochemical changes in a galactose-fed rat **model** for diabetic complications.
AUTHOR: Aukunuru Jithan V; Sunkara Gangadhar; Ayalasomayajula Surya P; Deruiter Jack; Clark Randall C; Kompella Uday B(a)
AUTHOR ADDRESS: (a)Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, 68198-6025**USA E-Mail: ukompell@unmc.edu
JOURNAL: Pharmaceutical Research (New York) 19 (3):p278-285 March, **2002**
MEDIUM: print
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose: To fabricate and characterize in vitro and in vivo performance of a sustained release biodegradable implant for N-4-(benzoylaminophenylsulfonyl glycine) (BAPSG), a novel aldose reductase inhibitor. Methods: The ability of BAPSG to inhibit aldose reductase activity and glucose-induced vascular **endothelial** growth factor (VEGF) expression was assessed in a **retinal** pigment epithelial **cell** line (ARPE-19). A poly (DL-lactic-co-glycolic acid) implant containing 50% w/w BAPSG was fabricated and characterized for drug loading, in vitro drug release, and the thermal behavior of the drug

and the polymer. Implants were injected subcutaneously into a galactose-fed diabetic rat **model** and cataract scores, plasma and tissue drug levels, galactitol levels in the lens and the **retina**, glutathione levels in the plasma, lens, cornea and **retina** and VEGF expression in the **retina** were determined on or until 18 days. Results: BAPSG inhibited aldose reductase activity and reduced VEGF expression in ARPE-19 **cells**. Implants (1X4 mm), with a loading efficiency of 106+-7% for BAPSG, were fabricated. Upon implant fabrication, while the glass transition temperature of the polymer decreased, the melting point of the drug was not affected. In vivo drug release correlated well with in vitro release, with apprx44% drug release occurring in vivo by the end of 18 days. The implant reduced galactitol accumulation, glutathione depletion, cataract scores, and VEGF expression in galactose-fed rats. Conclusions: An injectable biodegradable implant of BAPSG sustained drug release in vitro and in vivo, and reduced galactitol accumulation, glutathione depletion, cataract scores, and VEGF expression in galactose-fed rats.

2002

5/3,AB/56 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13616327 BIOSIS NO.: 200200245148
Pathologic features of vascular **endothelial** growth factor-induced **retinopathy** in the nonhuman primate.
AUTHOR: Tolentino Michael J; McLeod D Scott; Taomoto Makoto; Otsuji Tsuyoshi; Adamis Anthony P; Lutty Gerard A(a)
AUTHOR ADDRESS: (a)Wilmer Ophthalmological Institute, Johns Hopkins Hospital, 600 North Wolfe St., 170 Woods Research Building, Baltimore, MD, 21287-9115**USA E-Mail: glutty@jhmi.edu
JOURNAL: American Journal of Ophthalmology 133 (3):p373-385 March, **2002**
MEDIUM: print
ISSN: 0002-9394
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PURPOSE: Vascular **endothelial** growth factor (VEGF) is a potent ischemia-upregulated angiogenic protein that has been implicated in diabetic **retinopathy**. Intravitreal VEGF injections have not previously been shown to produce preretinal neovascularization. The purpose of this study was to further characterize the angiopathic changes that occur after intravitreal injections in a nonhuman primate and determine if preretinal neovascularization develops. DESIGN: Experimental animal study. METHODS: Vascular **endothelial** growth factor 165 was injected into the eyes of normal cynomolgus monkeys at regular intervals. As a control, normal eyes were injected with phosphate buffered saline. Color photography and fluorescein angiography were performed at regular intervals. The **retinas** were incubated for adenosine diphosphatase (ADPase) activity to visualize **retinal** vessels. The **retinas** were flat-embedded and areas of potential preretinal neovascularization were identified en bloc and serially sectioned. RESULTS: Areas of capillary nonperfusion and vessel dilation and tortuousity were seen by angiography. In serial sections, the nonperfused areas were found to be associated with **endothelial cell** hyperplasia in vessel lumens. Preretinal neovascularization originating only from superficial veins and venules was observed throughout peripheral **retina**, but was not seen in the posterior pole. Lacunae-like veins were subdivided by the process of intussusception and **endothelial cell** bridging. Arterioles demonstrated **endothelial cell** hyperplasia and

microaneurysms. CONCLUSION: Intraocular injections of VEGF were sufficient to produce preretinal neovascularization in the nonhuman primate. Most vasculopathic structures were associated with **endothelial cell** hyperplasia. These results demonstrate that VEGF alone can produce many features of both nonproliferative and proliferative diabetic **retinopathy** including the previously undescribed development of preretinal neovascularization. This well-characterized VEGF-induced primate **model** of **retinal** neovascularization may be useful as a means of testing new treatments for **retinal** neovascularization.

2002

5/3,AB/57 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13590870 BIOSIS NO.: 200200219691
Diabetes-induced nitrative stress in the **retina**, and correction by aminoguanidine.
AUTHOR: Du Yunpeng; Smith Mark A; Miller Casey M; Kern T S(a)
AUTHOR ADDRESS: (a)Clinical and Molecular Endocrinology, Department of Medicine, Case Western Reserve University, 10900 Euclid Avenue, 434 Biomedical Research Building, Cleveland, OH, 44106-4951**USA E-Mail: tsk@po.cwru.edu
JOURNAL: Journal of Neurochemistry 80 (5):p771-779 March, **2002**
MEDIUM: print
ISSN: 0022-3042
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Aminoguanidine inhibits the development of **retinopathy** in diabetic animals, but the mechanism remains unclear. Inasmuch as aminoguanidine is a relatively selective inhibitor of the inducible isoform of nitric oxide synthase (iNOS), we have investigated the effects of hyperglycemia on the **retinal** nitric oxide (NO) pathway in the presence and absence of aminoguanidine. In vivo studies utilized **retinas** from experimentally diabetic rats treated or without aminoguanidine for 2 months, and in vitro studies used bovine **retinal endothelial cells** and a transformed **retinal** glial **cell** line (rMC-1) incubated in 5 mM and 25 mM glucose with and without aminoguanidine (100 mug/mL). NO was detected as nitrite and nitrate, and nitrotyrosine and iNOS were detected using immunochemical methods. **Retinal** homogenates from diabetic animals had greater than normal levels of NO and iNOS ($p<0.05$), and nitrotyrosine was greater than normal, especially in one band immunoprecipitated from **retinal** homogenates. Oral aminoguanidine significantly inhibited all of these increases. Nitrotyrosine was detected immunohistochemically only in the **retinal** vasculature of non-diabetic and diabetic animals. **Retinal endothelial** and rMC-1 **cells** cultured in high glucose increased NO and NT, and aminoguanidine inhibited both increases in rMC-1 **cells**, but only NT in **endothelial cells**. Hyperglycemia increases NO production in **retinal cells**, and aminoguanidine can inhibit this abnormality. Inhibition of diabetic **retinopathy** by aminoguanidine might be mediated in part by inhibition of sequelae of NO production.

2002

5/3,AB/58 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

metastases of human gastrointestinal cancer **cells** such as the human stomach carcinoma line AZ-521 in animal **models**, and is currently in use in phase I cancer trials. However, the mechanism of its antimetastatic action is still poorly understood. Tumor metastasis depends on angiogenesis, and various **retinoids** have been found to exhibit antiangiogenic activity. Based on these findings we here examined the antiangiogenic effects of TAC-101. Oral administration of TAC-101 (2-8 mg/kg/day) resulted in a drastic suppression of the AZ-521 **cell**-induced angiogenesis in a mouse dorsal air sac assay system, compared to the vehicle alone. Immunohistochemical analysis with antibody against the **endothelial** marker CD31 revealed a significant reduction in microvessel density in liver metastases from animals treated with TAC-101 (8 mg/kg p.o.), compared to liver metastases from the untreated control animals. The ability of TAC-101 (8 mg/kg p.o.) to prevent experimental liver metastasis of AZ-521 **cells** in athymic nude mice was comparable with that of the known angiogenesis inhibitor TNP-470 (30 mg/kg s.c.). TAC-101 also affected angiogenesis in chorioallantoic membranes and some functions of **endothelial cells** associated with angiogenesis, whereas the **retinoid** failed to suppress AZ-521 **cell** proliferation directly. These data suggest that the TAC-101 is an orally active antiangiogenic agent and that this antiangiogenic property may contribute to its efficacy against liver metastasis of human stomach cancer **cells**.

2001

5/3,AB/60 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13149573 BIOSIS NO.: 200100356722
Immortalized **retinal** pigmentary epithelial **cell** lines and their applications.
AUTHOR: Greenwood John(a); Adamson Peter; Lund Raymond
AUTHOR ADDRESS: (a)London**UK
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1243 (1):pNo Pagination Feb. 6, **2001**
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The invention features immortalized **retina**-derived (**retinal endothelial** or **retinal** epithelial pigmentary) **cell** lines capable of being implanted in the **retina** and of carrying a **therapeutic** substance to the eye and to the central nervous system. Such lines can also be used as a **model** for studying blood central nervous system interfaces. These lines are derived from primary **retinal** cultures selected from the group consisting of primary **retinal endothelial cells** and primary **retinal** epithelial **cells**, comprise a nucleic acid fragment containing at least one immortalizing fragment of a heat-sensitive viral oncogene, which nucleic fragment is optionally associated with at least one selection gene, and have the morphological characteristics and at least the expression characteristics of the surface antigens of corresponding primary cultures.

2001

5/3,AB/61 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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13144413 BIOSIS NO.: 200100351562
Prevention of experimental laser induced choroidal neovascularization by intravitreal injection of AG3340.
AUTHOR: El-Bradey M H(a); Cheng L(a); Appelt K; Bartsch D U(a); Plummer D (a); Bergeron-Lynn G(a); Severson G M(a); Freeman W R(a)
AUTHOR ADDRESS: (a)Shiley Eye Ctr, UCSD, La Jolla, CA, 92093-0946**USA
JOURNAL: IOVS 42 (4):pS521 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

5/3,AB/62 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13115345 BIOSIS NO.: 200100322494
Effect of laser treatment of RPE and **retinal** glial **cells** in vitro on the permeability of **retinal** vascular **endothelial cell** monolayers.
AUTHOR: Tretiach M(a); Gillies M C(a)
AUTHOR ADDRESS: (a)Department of Clinical Ophthalmology, Save Sight Institute, Sydney, NSW**Australia
JOURNAL: IOVS 42 (4):pS207 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

5/3,AB/63 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13107604 BIOSIS NO.: 200100314753
Cyclic stretch and hypertension induce **retinal** expression of vascular **endothelial** growth factor and vascular **endothelial** growth factor receptor-2: Potential mechanisms for exacerbation of diabetic **retinopathy** by hypertension.
AUTHOR: Suzuma Izumi; Hata Yasuaki; Clermont Allen; Pokras Frank; Rook Susan L; Suzuma Kiyoshi; Feener Edward P; Aiello Lloyd Paul(a)
AUTHOR ADDRESS: (a)Joslin Diabetes Center, One Joslin Pl., Boston, MA, 02115: lpaiello@joslin.harvard.edu**USA
JOURNAL: Diabetes 50 (2):p444-454 February, **2001**
MEDIUM: print
ISSN: 0012-1797
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Systemic hypertension exacerbates diabetic **retinopathy** and other coexisting ocular disorders through mechanisms that remain largely

unknown. Increased vascular permeability and intraocular neovascularization characterize these conditions and are complications primarily mediated by vascular **endothelial** growth factor (VEGF). Because systemic hypertension increases vascular stretch, we evaluated the expression of VEGF, VEGF-R2 (kinase insert domain-containing receptor (KDR)), and VEGF-R1 (fms-like tyrosine kinase (Flt)) in bovine **retinal endothelial cells** (BRECs) undergoing clinically relevant cyclic stretch and in spontaneously hypertensive rat (SHR) **retina**. A single exposure to 20% symmetric static stretch increased KDR mRNA expression 3.9+-1.1-fold after 3 h (P=0.002), with a gradual return to baseline within 9 h. In contrast, BRECs exposed to cardiac-profile cyclic stretch at 60 cpm continuously accumulated KDR mRNA in a transcriptionally mediated, time-dependent and stretch-magnitude-dependent manner. Exposure to 9% cyclic stretch increased KDR mRNA expression 8.7+-2.9-fold (P=0.011) after 9 h and KDR protein concentration 1.8+-0.3-fold (P=0.005) after 12 h. Stretched-induced VEGF responses were similar. Scatchard binding analysis demonstrated a 180+-40% (P=0.032) increase in high-affinity VEGF receptor number with no change in affinity. Cyclic stretch increased basal thymidine uptake 60+-10% (P<0.001) and VEGF-stimulated thymidine uptake by 2.6+-0.2-fold (P=0.005). VEGF-NAb reduced cyclic stretch-induced thymidine uptake by 65%. Stretched-induced KDR expression was not inhibited by AT1 receptor blockade using candesartan. Hypertension increased **retinal** KDR expression 67+-42% (P<0.05) in SHR rats compared with normotensive WKY control animals. When hypertension was reduced using captopril or candesartan, **retinal** KDR expression returned to baseline levels. VEGF reacted similarly, but Flt expression did not change. These data suggest a novel molecular mechanism that would account for the exacerbation of diabetic **retinopathy** by concomitant hypertension, and may partially explain the principal clinical manifestations of hypertensive **retinopathy** itself. Furthermore, these data imply that anti-VEGF **therapies** may prove **therapeutically** effective for hypertensive **retinopathy** and/or ameliorating the deleterious effects of coexistent hypertension on VEGF-associated disorders such as diabetic **retinopathy**.

2001

5/3,AB/64 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13101715 BIOSIS NO.: 200100308864
Response of experimental **retinal** neovascularization to thiazolidinediones.
AUTHOR: Murata Toshinori; Hata Yasuaki; Ishibashi Tatsuro; Kim Sarah; Hsueh Willa A; Law Ronald E; Hinton David R(a)
AUTHOR ADDRESS: (a)Department of Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, 90033: dhinton@hsc.usc.edu**USA
JOURNAL: Archives of Ophthalmology 119 (5):p709-717 May, **2001**
MEDIUM: print
ISSN: 0003-9950
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Objective: To determine the effect of thiazolidinediones (TZDs) on experimental **retinal** neovascularization. Methods: The ability of the TZDs troglitazone and rosiglitazone maleate (1-20 mumol/L) to inhibit **retinal endothelial cell** (REC) proliferation, migration, tube formation, and signaling was determined in response to

vascular **endothelial** growth factor (VEGF). In vivo studies were performed using the oxygen-induced ischemia **model** of **retinal** neovascularization. Neonatal mice were treated with intravitreous injection of 0.5 muL of troglitazone (100 mumol/L) or rosiglitazone maleate (100 mumol/L), or vehicle, and **retinal** neovascularization was assayed qualitatively and quantitatively by means of angiography and histological examination. Results: Expression of the TZD receptor, peroxisome proliferator-activated receptor gamma, was confirmed in RECs by means of Western immunoblotting. Rosiglitazone and troglitazone inhibited VEGF-induced migration (P<.05), proliferation (P < .05), and tube formation (P<.01) by RECs in vitro beginning at 10 mumol/L. Rosiglitazone and troglitazone inhibited phosphorylation of extracellular signal-regulated mitogen-activated protein kinase 1 in RECs. Intravitreous injection of rosiglitazone or troglitazone inhibited development of **retinal** neovascularization (P<.01) but did not significantly inhibit VEGF overexpression in the ganglion **cell** layer of the ischemic **retina**. Conclusion: The TZDs inhibit experimental **retinal** neovascularization with an effect that is primarily downstream of VEGF expression. Clinical Relevance: The TZDs are widely prescribed and should be evaluated for their potential to inhibit the progression of diabetic **retinopathy**.
2001

5/3,AB/65 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13095324 BIOSIS NO.: 200100302473
Tissue-specific gene **therapy** directed to tumor angiogenesis.
AUTHOR: Varda-Bloom N; Shaish A; Gonen A; Levanon K; Greenbereger S; Ferber S; Levkovitz H; Castel D; Goldberg I; Afek A; Kopolovitc Y; Harats D(a)
AUTHOR ADDRESS: (a)Institute of Lipid and Atherosclerosis Research, Sheba Medical Center, Tel-Hashomer, 52621**Israel
JOURNAL: Gene Therapy 8 (11):p819-827 June, **2001**
MEDIUM: print
ISSN: 0969-7128
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Gene **therapy** directed specifically to the vascular wall, particularly to angiogenic **endothelial cells** is a prerequisite in vascular disease treatment. Angiogenesis is a major feature in many pathological conditions including wound healing, solid tumors, developing metastases, ischemic heart diseases and diabetic **retinopathy**. In the present study we developed a tissue-specific gene **therapy** to the angiogenic blood vessels of tumor metastasis using an adeno-based vector containing the murine preproendothelin-1 (PPE-1) promoter. Genes activated by the PPE-1 promoter were highly expressed in bovine aortic **endothelial cells** in vitro. Systemic injection of the adenoviral vectors AdPPE-1-luciferase and AdCMV-luciferase to normal C57BL/6 mice, resulted in higher activity of PPE-1 promoter compared with CMV promoter in the aorta and vascularized tissues such as heart, kidney, lung and pancreas. Systemic administration of the adenoviral vector, in mice bearing Lewis lung carcinoma, resulted in high and specific activity of PPE-1 in the new vasculature of primary tumors and lung metastasis. **Cellular** distribution of the delivered gene revealed highest expression of GFP in angiogenic **endothelial cells** of the metastasis. We expect that this approach of 'vascular-directed' gene **therapy** will be applicable to both vascular diseases and cancer.

2001

5/3,AB/66 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13080129 BIOSIS NO.: 200100287278
Estrogen may enhance VEGFR-2 expression in the process of laser-induced CNV formation.
AUTHOR: Tanemura M(a); Miyamoto N(a); Mandai M(a); Honda Y(a)
AUTHOR ADDRESS: (a)Ophthalmology Vis Sciences, Kyoto Univ Grad Sch Med, Sakyo-ku, Kyoto**Japan
JOURNAL: IOVS 42 (4):pS96 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

5/3,AB/67 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

13080101 BIOSIS NO.: 200100287250
Vascular **endothelial** growth factor and placental growth factor have distinct and critical roles during **retinal** vascular development and degeneration.
AUTHOR: Feeney S A(a); Simpson D A C(a); Gardiner T A(a); Boyle C(a); Jamison P(a); Archer D B(a); Stitt A W(a)
AUTHOR ADDRESS: (a)Ophthalmology, Queens Univ of Belfast, Belfast**UK
JOURNAL: IOVS 42 (4):pS90 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

5/3,AB/68 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13068444 BIOSIS NO.: 200100275593
Role of CD38/CD31 interactions in disease: The acute promyelocytic leukemia (APL) **model**.
AUTHOR: Deaglio Silvia(a); Dianzani Umberto(a); Ramenghi Ugo(a); Mehta Kapil; Malavasi Fabio(a)
AUTHOR ADDRESS: (a)University of Torino, via Santena 19, Torino, 10126** Italy
JOURNAL: FASEB Journal 15 (5):pA1029 March 8, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract

LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Human CD38, the prototype member of a new family of NAD metabolizing ectoenzymes, is a surface receptor mediating selectin-type adhesion with **endothelial cells** (HEC). Its HEC counterpart was recently identified and characterized as CD31. CD38/CD31 interactions induce on the CD38 side phosphorylation of cytoplasmic molecules, Ca2+ fluxes, activation of nuclear factors and synthesis and secretion of a panel of cytokines. Recently, we have investigated pathological **models** informative as to the biological significance of this interaction. APL is a myeloid leukemia characterized by the presence of a neoplastic clone which differentiates into granulocytes upon all-trans **retinoic** acid treatment (ATRA). As a relic of their tumor origin, differentiated **cells** express CD38 on their surface. A proportion of APL patients treated with ATRA develops a clinical picture of respiratory distress known as **retinoic** acid syndrome (RAS) and characterized by increased adhesion of CD38+ differentiated **cells** to lung HEC. The phenotype analysis of peripheral blood and bone marrow lymphocytes obtained from pediatric APL patients at different time points in the course of **therapy**, revealed that the differentiated **cells** maintain CD38 on the membrane for a period of over a year, independently of cycles of ATRA administration. Moreover, the CD38-related protein CD157 is also up-regulated in vivo in a way similar to CD38, while, in opposition to what observed for CD38, no increase in surface expression was seen using **cell** lines representative of APL. CD31 molecule is also up-regulated, thus the in vivo ATRA-differentiated **cells** express simultaneously CD38, its ligand CD31 and its sister-molecule CD157. Finally, a role for CD38 and CD31 in the differentiated **cells** adhesion to HEC was demonstrated using a dynamic adhesion system that enhances CD38-mediated binding. Addition of dexamethasone, the drug of choice in the treatment of RAS, impairs to some extent the early phases of adhesion to HEC.

2001

5/3,AB/69 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12988612 BIOSIS NO.: 200100195761
Dose response of rat **retinal** microvessels to proton dose schedules used clinically: A pilot study.
AUTHOR: Archambeau John O(a); Mao Xiao W; McMillan Paul J; Gouloumet Vanessa L; Oeinck Steven C; Grove Roger; Yonemoto Leslie T; Slater Jerry D; Slater James M
AUTHOR ADDRESS: (a)Department of Radiation Medicine, Loma Linda University Medical Center, 11234 Anderson Street, Loma Linda, CA, 92354: jarcham@lluci.llu.edu**USA
JOURNAL: International Journal of Radiation Oncology Biology Physics 48 (4):p1155-1166 November 1, **2000**
MEDIUM: print
ISSN: 0360-3016
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Purpose: This preclinical rat pilot study quantifies **retinal** microvessel, **endothelial**, and pericyte population changes produced by proton irradiation. Methods and Materials: The left eyes of rats were irradiated with single doses of 8, 14, 20, and 28 Gy protons; right eyes, with two fractions. Animals were euthanized, and

eyes were removed; elastase digests were prepared, and **cell** populations were counted in sample fields. Results were compared with unirradiated controls. Results: Progressive time- and dose-dependent **endothelial cell** loss occurred following all schedules. **Cell** loss was significantly different from control values ($p < 0.001$) following 28 Gy and following 20 Gy ($p < 0.05$) in a single dose. **Endothelial cell** loss was the same for single- and split-dose schedules. Progressive **endothelial cell** loss produced vessel collapse and acellular vessel strands. **Endothelial cells** were in the Go phase of the mitotic cycle. 28 Gy produced photoreceptor **cell** loss. Conclusion: The **retinal** digest is an elegant bioassay to quantify the microvessel population response. Single- and split-dose schedules appear to yield similar outcomes, in terms of **endothelial cell** density.

2000

5/3,AB/70 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

12967797 BIOSIS NO.: 200100174946
Immortalized **retinal cell** lines and their applications.
AUTHOR: Greenwood John(a); Adamson Peter; Lund Raymond
AUTHOR ADDRESS: (a)London**UK
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1236 (3):pNo Pagination July 18, **2000**
MEDIUM: e-file
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Immortalized **cell** lines of **retinal** origin (**retinal endothelial** and **retinal** pigmentary epithelial origin) which are capable of being implanted in the **retina** and of conveying a substance of **therapeutic** interest into the eye and the central nervous system. Such lines can also serve as a **model** for studying the blood/central nervous system interfaces. These lines are derived from primary cultures of **retinal cells** selected from the group comprising the primary **retinal endothelial cells** and the primary **retinal** epithelial **cells**, comprise a nucleic acid fragment containing at least one immortalizing fragment of a heat-sensitive viral oncogene, which nucleic acid fragment may be associated with at least one selection gene, and exhibit the morphological characteristics and at least the surface antigen expression characteristics of the corresponding primary culture **cells**.

2000

5/3,AB/71 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12879148 BIOSIS NO.: 200100086297
Diabetic **endothelial** dysfunction: The role of poly(ADP-ribose) polymerase activation.
AUTHOR: Soriano Francisco Garcia; Virag Laszlo; Jagtap Prakash; Szabo Eva; Mabley Jon G; Liaudet Lucas; Marton Anita; Hoyt Dale G; Murthy Kanneganti G K; Salzman Andrew L; Southan Garry J; Szabo Csaba(a)
AUTHOR ADDRESS: (a)Inotek Corporation, Suite 419E, 100 Cummings Center, Beverly, MA, 01915: szabocsaba@aol.com**USA

JOURNAL: Nature Medicine 7 (1):p108-113 January, **2001**
MEDIUM: print
ISSN: 1078-8956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Diabetic patients frequently suffer from **retinopathy**, nephropathy, neuropathy and accelerated atherosclerosis. The loss of **endothelial** function precedes these vascular alterations. Here we report that activation of poly(ADP-ribose) polymerase (PARP) is an important factor in the pathogenesis of **endothelial** dysfunction in diabetes. Destruction of islet **cells** with streptozotocin in mice induced hyperglycemia, intravascular oxidant production, DNA strand breakage, PARP activation and a selective loss of endothelium-dependent vasodilation. Treatment with a novel potent PARP inhibitor, starting after the time of islet destruction, maintained normal vascular responsiveness, despite the persistence of severe hyperglycemia. **Endothelial cells** incubated in high glucose exhibited production of reactive nitrogen and oxygen species, consequent single-strand DNA breakage, PARP activation and associated metabolic and functional impairment. Basal and high-glucose-induced nuclear factor-kappaB activation were suppressed in the PARP-deficient **cells**. Our results indicate that PARP may be a novel drug target for the **therapy** of diabetic **endothelial** dysfunction.

2001

5/3,AB/72 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12878486 BIOSIS NO.: 200100085635
Influence of laser photocoagulation on choroidal capillary cytoarchitecture.
AUTHOR: Guymer Robyn H(a); Hageman Gregory S; Bird Alan C
AUTHOR ADDRESS: (a)Department of Ophthalmology, Melbourne University, Centre for Eye Research Australia, 32 Gisborne Street, East Melbourne, VIC, 3002: guymer@cera.unimelb.edu.au**Australia
JOURNAL: British Journal of Ophthalmology 85 (1):p40-46 January, **2001**
MEDIUM: print
ISSN: 0007-1161
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Aim: To identify if laser photocoagulation induces morphological changes specifically related to the choroidal capillary **endothelial** processes that protrude into Bruch's membrane. Methods: Two human eyes and one adult macaque monkey eye received **retinal** laser photocoagulation that was just suprathreshold, before enucleation or exenteration. They were examined by electron microscopy to determine the length of the **endothelial** processes emanating from the choroidal capillaries in the region around the laser burn. One human and two monkey untreated eyes were used for comparison. Results: In human eyes, there was no increase in the number of processes 15 hours after laser treatment but at 5 days the processes were more numerous and longer within 400-500 mum of the burn than in the untreated half of the same eye. The processes were longer 9 days after photocoagulation in the monkey, when compared with untreated monkeys, and some breached the elastic lamina, a

phenomenon not seen in the untreated eyes. Qualitative differences were also noted in the **endothelial cell** processes following photocoagulation. Neovascularisation was not observed. Conclusions: Protrusion of choroidal **endothelial cell** processes into Bruch's membrane is a normal anatomical feature but the number, length, and morphology of the processes change following mild photocoagulation. It is plausible that these processes may play a part in the clearance of debris from Bruch's membrane, and represent an early stage of angiogenesis. If the latter is true prophylactic laser photocoagulation at just suprathreshold levels may carry a risk of inducing choroidal neovascularisation.

2001

5/3,AB/73 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12836664 BIOSIS NO.: 200100043813
Rank of gene **therapy** in cardiovascular diseases.
ORIGINAL LANGUAGE TITLE: Stellenwert der Gentherapie in der kardiovaskulaeren Medizin.
AUTHOR: Auer Johann(a); Berent Robert; Schleicher Karin; Eber Bernd
AUTHOR ADDRESS: (a)II. Interne Abteilung mit Kardiologie und Internistische Intensivmedizin, Allgemeines offentliches Krankenhaus der Barmherzigen Schwestern vom Hl. Kreuz, Grieskirchner Strasse 42, A-4600, Wels: johann.auer@khwels.at**Austria
JOURNAL: Herz 25 (7):p635-642 November, **2000**
MEDIUM: print
ISSN: 0340-9937
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: English; German

ABSTRACT: Vascular gene transfer potentially offers new treatments for cardiovascular diseases. It may be used to overexpress **therapeutically** important proteins and correct genetic defects, and to test experimentally the effects of various genes in a local vascular compartment. Vascular **endothelial** growth factor (VEGF) and fibroblast growth factor (FGF) gene transfers have improved blood flow and collateral development in ischemic limb and myocardium. Promising **therapeutic** effects have been obtained in animal **models** of restenosis or vein-graft thickening with the transfer of genes coding for VEGF, nitric-oxide synthase, thymidine kinase, **retinoblastoma**, growth arrest homoeobox, tissue inhibitor of metalloproteinases, cyclin or cyclin-dependent kinase inhibitors, fas ligand and hirudin, and antisense oligonucleotides against transcription factors or **cell** -cycle regulatory proteins. First experiences of VEGF gene transfer and decoy oligonucleotides in human beings have been reported. However, further developments in gene transfer vectors, gene delivery techniques and identification of effective treatment genes will be required before the full **therapeutic** potential of gene **therapy** in cardiovascular disease can be assessed.

DESCRIPTORS:
2000

5/3,AB/74 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12813936 BIOSIS NO.: 200100021085
Inhibition of VEGF-mediated angiogenesis by antisense gene **therapy**: Role of Flk-1 and Flt-1 receptors.
AUTHOR: Sirois M G(a); Marchand G S(a); Noiseux N(a)
AUTHOR ADDRESS: (a)Montreal, PQ**Canada
JOURNAL: Canadian Journal of Cardiology 16 (Supplement F):p155F-156F September, **2000**
MEDIUM: print
CONFERENCE/MEETING: 53rd Annual Meeting of the Canadian Cardiovascular Society Vancouver, British Columbia, Canada October 20-November 01, 2000
SPONSOR: Canadian Cardiovascular Society
ISSN: 0828-282X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

5/3,AB/75 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12763781 BIOSIS NO.: 200000517404
Angiogenesis and vasculogenesis. **Therapeutic** approaches for stimulation of post-natal neovascularization.
AUTHOR: Kalka Christoph(a); Asahara Takayuki; Krone Wilhelm; Isner Jeffrey M
AUTHOR ADDRESS: (a)Cardiovascular Research, St. Elizabeth's Medical Center, 736 Cambridge Street, Boston, MA, 02135**USA
JOURNAL: Herz 25 (6):p611-622 September, **2000**
MEDIUM: print
ISSN: 0340-9937
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: English; German

ABSTRACT: The formation of new blood vessel is essential for a variety of physiological processes like embryogenesis and the female reproduction as well as wound healing and neovascularization of ischemic tissue. Major progress in understanding the underlying mechanisms regulating blood vessel growth has offered novel **therapeutic** options in the treatment of a variety of diseases including ischemic cardiovascular disorders. Vasculogenesis and angiogenesis are the mechanisms responsible for the development of the blood vessels. Angiogenesis refers to the formation of capillaries from preexisting vessels in the embryo and adult organism. While pathologic angiogenesis includes the role of post-natal neovascularization in the pathogenesis of arthritis, diabetic **retinopathy**, and tumor growth and metastasis, **therapeutic** angiogenesis, either endogenously or in response to administered growth factors, includes the development of collateral blood vessels in tissue ischemia. Preclinical studies established that angiogenic growth factors could promote collateral artery development in animal **models** of peripheral and myocardial ischemia. Subsequent clinical trials using gene transfer of naked DNA encoding for VEGF for the treatment of critical limb and myocardial ischemia documented the safety and clinical benefit of this novel **therapeutic** approach. Several objective methods indicated marked improvement in collateral vessel development. Vasculogenesis describes the development of new blood vessels from in situ differentiating **endothelial cells**. Recently considered to be restricted to embryogenesis, there exists now striking evidence that **endothelial** progenitor **cells** (EPC) circulate also in adult peripheral blood able to participate in ongoing neovascularization. Different cytokines and growth factors have a stimulatory effect on these

bone-marrow derived EPC. Granulocyte macrophage colony stimulating factor (GM-CSF) and vascular **endothelial** growth factor (VEGF) mobilize EPC from the bone marrow into the peripheral circulation. While their endogenous contribution to postnatal neovascularization needs to be documented, the iatrogenic expansion and mobilization of EPC might represent an effective means to augment the resident population of **endothelial cells** (ECs). This kind of **cell therapy** for tissue regeneration in ischemic cardiovascular diseases opens a novel and challenging clinical option besides or in addition to the use of growth factors in gene **therapy**.

2000

5/3,AB/76 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12646057 BIOSIS NO.: 200000399559
Selective upregulation of fibroblast Fas ligand expression, and prolongation of Fas/Fas ligand-mediated skin allograft survival, by **retinoic** acid: The skin as a **retinoide**-inducible immune privilege site.
AUTHOR: Saitoh Atsushi; Kawanabe Takeshi; Weidong He; Kayagaki Nobuhiko; Kawamura Tatsuyoshi; Yagita Hideo; Okumura Ko; Shimada Shinji(a)
AUTHOR ADDRESS: (a)Department of Dermatology, Yamanashi Medical University, Shimokato, Tamaho, Nakakoma, Kofu, Yamanashi, 409-3898**Japan
JOURNAL: Journal of Investigative Dermatology 115 (2):p154-161 August, **2000**
MEDIUM: print
ISSN: 0022-202X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Fas/Fas ligand-mediated lymphocyte apoptosis has been implicated in the suppression of immune responses and may cause immune privilege. Human corneas exhibit immune privilege and can be transplanted across allogeneic barriers without immunosuppressive **therapy**, perhaps, because corneal keratinocytes express Fas ligand. To characterize Fas and Fas ligand expression in skin, we examined expression by murine keratinocytes, dermal fibroblasts, melanocytes, and human umbilical **endothelial cells**. We also studied the regulation of Fas and Fas ligand in skin **cells** by **retinoic** acid, vitamin D3, and dexamethasone as well as various cytokines. Among the molecules and **cells** tested, **retinoic** acid selectively upregulated the expression of Fas ligand molecule by fibroblasts. **Retinoic** acid-induced Fas ligand+ fibroblasts killed Fas+ target **cells**, and this killing was blocked by anti-Fas ligand antibody. The function of Fas ligand on dermal fibroblasts in vivo was tested in a cutaneous allograft system. Histoincompatible BALB/C mouse (H-2d) donor skin was grafted on to allogeneic C57BL/6 mice (H-2b). Daily local injection of **retinoic** acid blocked inflammation and extended graft survival for more than 10 d. Injection of **retinoic** acid into Fas ligand mutated gld/gld donor skin did not prevent leukocyte infiltration into the allograft or prolong graft survival. These experiments indicate that, in skin, **retinoic** acid selectively increases Fas ligand expression by fibroblasts and that **retinoic** acid has potent Fas/Fas ligand-dependent immunosuppressive activity.
2000

5/3,AB/77 (Item 26 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)
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12506524 BIOSIS NO.: 200000260026
Microvessel density, p53, **retinoblastoma**, and chromogranin A immunohistochemistry as predictors of disease-specific survival following radical prostatectomy for carcinoma of the prostate.
AUTHOR: Krupski Tracey; Petroni Gina R; Frierson Henry F Jr; Theodorescu Dan(a)
AUTHOR ADDRESS: (a)Department of Urology, University of Virginia Health Sciences Center, Charlottesville, VA, 22908**USA
JOURNAL: Urology 55 (5):p743-749 May, **2000**
MEDIUM: print.
ISSN: 0090-4295
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Objectives: Angiogenesis has been shown to be related to p53 and **retinoblastoma** gene function as well as to neuroendocrine differentiation (as measured by chromogranin A staining) in prostate tumors. Studies have indicated that immunohistochemical assessment of p53, **retinoblastoma**, and chromogranin A in prostate cancers treated by radical prostatectomy can be useful in predicting disease-specific survival, whereas the degree of microvessel density (MVD), a measure of angiogenesis, correlates with disease recurrence. The ability of MVD, however, to predict disease-specific survival either alone or in conjunction with other prognostic factors has not yet been evaluated. The purpose of our study was to determine the relative importance of p53, **retinoblastoma**, and chromogranin A as well as MVD in the prediction of disease-specific survival following radical prostatectomy in conjunction with classical pathologic assessment. Methods: From 1970 to 1984, radical prostatectomy was performed on 75 patients with clinical Stage A2 to B2 adenocarcinoma of the prostate. No neoadjuvant or adjuvant treatments were given, and patients were followed until death. Prostatectomy specimens were examined to evaluate conventional pathologic parameters. In addition, the tissue was immunohistochemically stained for p53, **retinoblastoma**, chromogranin A, and **endothelial cells**. A previously described computerized imaging system analyzed the microvessels and computed both "optimized" and "area-weighted" MVD scores. Proportional hazard **models** were used to investigate the simultaneous association of these variables with disease-specific survival. Results: Of the 75 patients, 4 had follow-up of less than 3 months, and 29 patients had inadequate tissue for analysis of all immunohistochemical markers. The analyzed subset of 42 patients was found to be representative of the cohort of 71 patients. Multivariate analysis revealed that p53 and **retinoblastoma** have the greatest prognostic importance regarding disease-specific survival. Chromogranin A and optimized or area-weighted MVD scores were of no additional value when p53 and **retinoblastoma** were assessed. Conclusions: Microvessel density, as a determinant of angiogenesis and chromogranin A, does not seem to add significantly to the prognostic disease-specific survival information provided by conventional pathology combined with p53 and **retinoblastoma** assessment.

2000

5/3,AB/78 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12446894 BIOSIS NO.: 200000200396

Integrin-mediated neutrophil adhesion and **retinal** leukostasis in diabetes.
AUTHOR: Barouch Fina Canas; Miyamoto Kazuaki; Allport Jennifer R; Fujita Kenji; Bursell Sven-Erik; Aiello Lloyd Paul; Luscinskas Francis William; Adamis Anthony P(a)
AUTHOR ADDRESS: (a)Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA, 02114**USA
JOURNAL: IOVS 41 (5):p1153-1158 April, **2000**
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Purpose. A critical early event in the pathogenesis of diabetic **retinopathy** is leukocyte adhesion to the diabetic **retinal** vasculature. The process is mediated, in part, by intercellular adhesion molecule-1 (ICAM-1) and results in blood-**retinal** barrier breakdown and capillary nonperfusion. This study evaluated the expression and function of the corresponding ICAM-1-binding leukocyte beta2-integrins in experimental diabetes. Methods. Diabetes was induced in Long Evans rats with streptozotocin. The expression of the surface integrin subunits CD11a, CD11b, and CD18 on rat neutrophils isolated from peripheral blood was quantitated with flow cytometry. In vitro neutrophil adhesion was studied using quantitative **endothelial cell**-neutrophil adhesion assays. The adhesive role of the integrin subunits CD11a, CD11b, and CD18 was tested using specific neutralizing monoclonal antibodies. CD18 bioactivity was blocked in vivo with anti-CD18 F(ab')2 fragments, and the effect on **retinal** leukocyte adhesion was quantitated with acridine orange leukocyte fluorography. Results. Neutrophil CD11a, CD11b, and CD18 surface integrin levels were 62% (n = 5, P = 0.006), 54% (n = 5, P = 0.045), and 38% (n = 5, P = 0.009) greater in diabetic versus nondiabetic animals, respectively. Seventy-five percent more neutrophils from diabetic versus nondiabetic animals adhered to rat **endothelial cell** monolayers (n = 6, P = 0.02). Pretreatment of leukocytes with either anti-CD11b or anti-CD18 antibodies lowered the proportion of adherent diabetic neutrophils by 41% (n = 6, P = 0.01 for each treatment), whereas anti-CD11a antibodies had no significant effect (n = 6, P = 0.5). In vivo, systemic administration of anti-CD18 F(ab')2 fragments decreased diabetic **retinal** leukostasis by 62% (n = 5, P = 0.001). Conclusions. Neutrophils from diabetic animals exhibit higher levels of surface integrin expression and integrin-mediated adhesion. In vivo, CD18 blockade significantly decreases leukostasis in the diabetic **retinal** microvasculature. Integrin adhesion molecules may serve as **therapeutic** targets for the treatment and/or prevention of early diabetic **retinopathy**.

2000

5/3,AB/79 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12410347 BIOSIS NO.: 200000163849
Expression of vascular **endothelial** growth factor and basic fibroblast growth factor after **retinal** photocoagulation in rats.
AUTHOR: Hagiwara Yoshiyuki(a)
AUTHOR ADDRESS: (a)Department of Ophthalmology, Osaka City University Medical School, Osaka**Japan
JOURNAL: Journal of the Osaka City Medical Center. 48 (3-4):p443-450 Dec., **1999**
ISSN: 0386-4103
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: Japanese; Non-English
SUMMARY LANGUAGE: English; Japanese

ABSTRACT: **Retinal** photocoagulation is used clinically to cause regression of **retinal** neovascularization and **retinal** edema. However, intense or even moderate photocoagulation can produce complications such as cystoid macular edema and choroidal neovascularization during tissue repair. Vascular **endothelial** growth factor (VEGF) and basic fibroblast growth factor (b-FGF) cause vascular hyperpermeability or neovascularization during scar formation. In this study of the relations between these growth factors and such complications, photocoagulation of mild to moderate intensity was used on 240 eyes of normal rats, and the concentrations of messenger RNAs (mRNAs) coding for VEGF and b-FGF in the **retina** and choroid were measured after 3, 24, 48, and 96 hours after photocoagulation by northern blotting. Vimentin mRNA expression was also studied as a maker of scar formation by glial **cells**, migrating fibroblasts, and **retinal** pigment epithelial **cells**. Histological exmamination of 4 eyes were done at the same times. Three hours after photocoagulation, glial **cells** had not proliferated, and vimentin mRNA had not increased in **retina**, compared with control. However, **retinal** VEGF mRNA at 3 hours was significantly higher than normal rat **retina**. Twenty-four hours after photocoagulation, the concentration of vimentin mRNA in the **retina** was higher than control, but VEGF in the **retina** was lower than control. The concentration of b-FGF was maximum at 24 hours, but vimentin mRNA was maximum at 48 hours, when VEGF and b-FGF mRNAs at 48 hours had decreased compared with their peak points. Throughout the experiment, mRNAs of VEGF and b-FGF in the choroid were unchanged. These findings suggest that **retinal** VEGF has an important role in sub-**retinal** exudate formation, which was seen in the histological examination immediately after photocoagulation. The results may reflect the participation of **retinal** b-FGF in glial proliferation in the **retina** during scar formation after photocoagulation.

1999

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Modulation of **endothelial cell** proliferation by **retinoid** x receptor agonists.
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JOURNAL: European Journal of Pharmacology 385 (2-3):p255-261 Dec. 3, **1999**
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ABSTRACT: One feature that contraindicates the wide **therapeutic** use of natural **retinoids** is their adverse effects during systemic use and the lack of receptor selectivity. In contrast, synthetic **retinoids** are distinguishable from each other on the basis of their partial or exclusive preference in binding and activation of selective **retinoid** receptors. We examined the inhibitory activities of natural and synthetic **retinoids** for their ability to reverse basic

demonstrated for cognitive functions, particularly for memory loss, attention, alertness, vigilance, arousal and mental fluidity. Some clinical studies have showed that EGb 761 treatment may improve the capacity of geriatric patients to cope with the stressful demands of daily life. The explanation is a dual stress-alleviating action of EGb 761: its facilitates behavioral adaptation to stress and may decrease the excess of cortisol release to stress. Moreover, EGb 761 shows a specific neuroprotective effects to hippocampic **cells**. Regarding the visual system, experimental studies have shown that EGb 761 can inhibit or reduce the functional **retinal** impairments resulting from ischemia-reperfusion, photodegeneration, diabetic or proliferative **retinopathy**. Clinical studies have revealed that EGb 761 may be useful in treating visual activity impairments and damages to the visual field associated with chronic cerebrovascular insufficiency, senile macular degeneration and diabete mellitus. Regarding the vestibular and auditory systems, experimental and clinical studies have shown the efficacy of EGb 761 in treating hypoacusis, tinnitus, vertigo, dizziness and other symptoms of vestibulocochlear disorders. At least, adequatly controlled studies in patients with peripheral arterial occlusive disease have provided good evidence for **therapeutic** efficacy in intermittent claudication. The future of EGb 761 is undoubtedly in the promise in slowing the progression of Alzheimer's disease. Indeed, two recent american clinical studies have shown the efficacy and safety of EGb 761 in patients with mild to severe Alzheimer's disease and multi-infarct dementia. In clinical terms, progression of symptoms was delayed by approximately 6 months. Actually new clinical studies are undertaken in USA and Europe. At the dawn of the third millenium (the Sixth for Ginkgo biloba) we propose a state of art about it.

1999

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11991175 BIOSIS NO.: 199900271694
Effects of a hematoporphyrin derivative on cultured rabbit corneal epithelial, stromal and **endothelial cells** under exposure to light.
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fibroblast growth factor-induced **endothelial cell** proliferation. Both the naturally occurring **retinoids** at nanomolar concentrations reversed basic fibroblast growth factor-induced **endothelial cell** proliferation. Among the synthetic **retinoids** tested, **retinoic** acid receptor/**retinoid** x receptor pan-agonist AGN 191659 ((E)-5-(2-(5,6,7,8-tetrahydro-3, 5,5,8,8-pentamethyl-2-naphtyl) propen-1-yl)-2-thiophenecarboxylic acid) and **retinoid** x receptor pan-agonist AGN 191701 ((E)-2-(2-(5,6,7,8-tetrahydro-3, 5,5,8,8-pentamethyl-2-naphthyl) propen-1-yl)-4-thiophenecarboxylic acid) at nanomolar concentrations reversed the basic fibroblast growth factor-induced **endothelial cell** proliferation. Since none of the **retinoic** acid receptor agonists tested had any effect, the inhibitory effect of AGN 191659 could be attributed to its **retinoid** x receptor receptor activity. These results suggest that **retinoid** x receptor agonists may be more selective anti-angiogenic agents due to their ability to inhibit **endothelial cell** proliferation.

1999

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12165015 BIOSIS NO.: 199900459864
Ginkgo biloba extract (EGb 761): A state of art at the dawn of the third millenium.
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JOURNAL: Annales Pharmaceutiques Francaises 57 (SUPPL. 1):p1S8-1S88 July, **1999**
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LANGUAGE: French; Non-English
SUMMARY LANGUAGE: English; French

ABSTRACT: EGb 761 is a standardized extract of dried leaves of Ginkgo biloba containing 24% ginkgo-flavonol glycosides, 6% terpene lactones such as ginkgolides A, B, C, J and bilobalide. Its broad spectrum of pharmacological activities allows it to be in adequacy to the numerous pathological requirements - hemodynamic, hemorheological, metabolic - which occur in cerebral, **retinal**, cochleovestibular, cardiac or peripheral ischemia. Moreover, EGb 761 has direct effects against necrosis and apoptosis of neurons and improves neural plasticity as evidenced in vestibular compensation. At the molecular and the **cellular** levels, some evidence obtained with animal **models** indicates that EGb 761 can interact as a free radical-scavenger and a inhibitor of lipid peroxydation with all, or nearly all reactive oxygen species; maintains ATP content by a protection of mitochondrial respiration and preservation of oxidative phosphorylations; exerts arterial and venous vasoregulator effects involving the releaseof **endothelial** factors and the catecholaminergic system. Moreover, EGb 761 regulates ionic balance in damaged **cells** and exerts a specific and potent Platelet-activating factor antagonist activity. Numerous well-controlled clinical studies, realized in Europe and in USA, have revealed that EGb 761 is an effective **therapy** for a wide variety of disturbances of cerebral function, ranging from cerebral impairment of ischemic vascular origins (ie multi infarct dementia), early cognitive decline to mild-to-moderate cases of the more severe types of senile dementias (including Alzheimer's disease) or mixed origins (ie psychoorganic origin). Improvement of signs and symptoms have been